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FROM PAEDIATRIC TO YOUNG ADULT IN AUTISTIC PATIENTS: HEALTHCARE SERVICES UTILISATION IN THE TRANSITION-AGE

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Keywords: Autism spectrum disorder; Epidemiology; Administrative databases; Health Outcomes; c

FROM PAEDIATRIC TO YOUNG ADULT IN AUTISTIC PATIENTS: HEALTHCARE SERVICES UTILISATION IN THE TRANSITION-AGE

Objectives: The purpose of this paper is provide an estimate of the prevalence rate of autism spectrum disorder (ASD) at 8 years of age in 2017 and investigate the change in healthcare services use during the transition-age.

Design: Longitudinal retrospective cohort study

Setting: Administrative Healthcare Database (2010-2017) in Italy

Participants: We identified 5,607 patients , 331 patients were recruited at 18 years old and the health service utilisation between the two years preceding and succeeding the 18th were investigated.

Interventions: none

Primary and secondary outcome measures: Prevalence rate and percentage of patients receiving healthcare services

Results: Prevalence at 8 was 5.4/1,000. Global access to health and social services decrease both before and after aged 18 (46.5% at 16, 68% at 18, 54.1% at 20). The percentage of patients receiving a neuropsychiatric visit decreases after aged 18 (30.8% at 18, 5.4% at 20). The utilisation of rehabilitation services decreased with age, going from 17.8% to 1.8%. Psychiatric outpatient services remained stable (about 14%). Territorial-based psychiatry services utilisation rate increased over 18 years of age. Considering psychiatric visits both in outpatient and territorial-based services, a rate increase was observed from 17.8% aged 18 to 25.4% at 20.

Conclusions: Our finding suggested that ASD patients changed "therapeutic references" with age from neuropsychiatric and rehabilitative services towards psychiatric and community-based services.

Strengths and limitations of this study.

- Longitudinal retrospective cohort study based on Administrative Healthcare Database: real-word diagnostic patterns of a large and unselected population
- Diagnosis was not validated
- Prevalence and incidence estimation
- Estimation of differences in rates of comorbidity and healthcare services utilisation in a selected retrospective longitudinal cohort of ASD patients from 16 to 20 years old

Keywords: Autism spectrum disorder; Epidemiology; Administrative databases; Health Outcomes; Health Service Research

INTRODUCTION

Autism spectrum disorder (ASD) is a brain-based chronic neurodevelopmental disorder, with lifelong impacts, characterised and diagnosed by impairments in social communication and social interaction with the presence of restricted, repetitive behaviours or interest [1]. ASD is a serious condition resulting in a significant burden for individuals, families and society [2,3]. Onset of ASD typically occurs by age 3, although some studies suggest that symptoms can emerge between 6 and 18 months of age and may not be full manifested until school age [4,5]. Children, adolescents and adults with ASD can often present a number of comorbidities including psychiatric conditions, intellectual disabilities, development delay, epilepsy, anxiety, language and motor difficulties and depression [6–9]. Moreover, an increase in mortality has been observed compared with the general population [10].

The aetiology of ASD remains largely unexplained. It seems to be highly hereditable [11] and some environmental risk factors [12] and parental age [13] may be involved [14]. The prevalence of ASD has increased in the last decades, although the reasons for this increase are not fully understood. It might be related to etiologic, non-etiologic and administrative factors (e.g. alternated diagnostic criteria, improved access at services and increased public and scientific interest [8,15,16]).

In 2010, [17] the prevalence rate for children aged 8 was estimated to be 3.9 per 1000 for boys and 0.8 per 1000 for girls. The annual incidence rates in 2010 [18] in children aged 2-8 was 1.02 per 1000 in boys aged 2-8 and 0.21 per 1000 in girls.

A review published in 2012 [19] estimated the global prevalence of ASD to be about 1% (62/10000); a more recent study has estimated the prevalence to be 1.5 in developed countries [14,17,20]. In 2014 [20] a prevalence rate of 16.8 per 1000 was estimated for children aged 8.

Treatments of ASD vary across the word and even within country regions and it seems that parents with a lower educational level are less successful in obtaining specialist interventions that could improve the outcome [8]. Treatments of ASD include early parent-mediated interventions, behavioural and social treatment. Evidence based pharmacology in ASD is currently limited to the treatment of co-occurring behaviour or diagnosis and not ASD itself [8]. Risperidone [21], Aripiprazole [22] have improved symptoms of irritability or agitation in children and adolescents with ASD. Methylphenidate [23] , Atomoxetine [24] Guafacine [25] have shown a benefit for ADHD symptoms in ASD. However, the use of such drugs presents some adverse effects and their use has been indicated during a specific age period.

While autism is generally considered a disorder of childhood, the rise in ASD prevalence in the last decades in children is resulting in an increased number of subject with ASD transitioning from paediatric to young adult medical services and this means that autism is rapidly becoming a disorder of adulthood as well [26]. There are evidences that for young people with special healthcare needs, such as autism, transitioning form paediatric to adult healthcare remains a problem [27,28]. The transition process may be especially difficult for young people whose special healthcare needs involve mental health, development disabilities of intellectual disabilities [28]. Moreover, the lack of clarity on adult ASD treatment guidelines increases the complexity of healthcare delivery and a involves a problematic transition from paediatric to adult healthcare [29].

Administrative claims data can be plentiful, comprehensive, cost efficient and free from some of biases that accompany other types of data, such as surveys or self-reports [30]. Analyses of administrative healthcare databases have the potential to include large number of subjects and have been successfully used in the study of health outcomes associated with a variety of conditions [30,31]. Studies conducted in US [32] and Canada [33,34] indicated that administrative claims data were able to clearly identify children with ASD.

The purpose of this paper is to use administrative databases derived from the largest Northern Italian population to a) provide an estimate of the prevalence of ASD at 8 years of age and b) investigate the change in healthcare services use by ASD patient during the transitioning from paediatric towards young adult healthcare services.

METHODS

Data collection

A retrospective cohort study was conducted using the Administrative Healthcare Database of the Health Protection Agency of the Metropolitan City of Milan (AHD-ATS) from January 1, 2010 to December 31, 2017. Only data regarding patients residing in the ATS were considered. In Italy, the National Healthcare System (NHS) is universal and fully covers the population and the ATS provides care to about 3,500,000 inhabitants.

Data were obtained from AHD-ATS, which included 8 different databases: 1) outpatient (6 millions records), 2) hospital discharge (1 million records), 3) co-payment Exemption Register (1 million), 4) emergency department (ED) accesses (2 millions), 5) rehabilitation interventions database (800,000 records), 6) territorial-based psychiatry interventions database (100,000 records), 7) pharmaceutical prescription databases (200 millions) and; 8) community and social services (CSS) (1 million records).

These databases can be linked through a unique identifier code; demographic information was obtained by record linkage using a unique identifier code with patients master data and Deprivation Index by using record linkage with 2001 General Census of Population and Housing.

ASD patients were defined as the subjects having reported a diagnosis of ASD (ICD-9 codes 299.00 to 299.99 or their ICD-10 equivalents) at least in one of the database during the study period [34]. For each patient, the calendar year of birth was used as an approximated age value at the time of services utilisations.

Statistical analysis

Prevalence and incidence rates estimation

Prevalence rates at 8 and 2-8 year incidence rates were estimated for 2017. The prevalence rate was obtained by dividing the number of children 8 years old diagnosed as ASD in 2017 or previously, by the population size – of the same age – in the ATS area as at 1 January, 2018 based on ISTAT data.

The annual incidences rates were obtained dividing the annual number of children aged 2-8 years newly diagnosed, by the general population subtracting the ASD number diagnosed in preceding years. Binomial 95% confidence intervals (95% CI) were calculated for the prevalence and incidence rate.

Consumptions and outcome models

We selected ASD patients from 2012 to 2015 in the calendar year of their 18th birthday, and we investigated the health service utilisation during a 5-year period: between the two years preceding and succeeding the 18$^{th\ year}$ (i.e. aged from 16 to 20). In details, we investigated the percentage of co-occurred conditions related to other psychiatric disease: as outcome, we investigated access to services (i.e. outpatients, rehabilitation interventions and community/social services, ED access, hospital admission, neuroleptic drugs consumption).

Co-occurring conditions were identified by using the chronicity database [35] that covers the 13 main comorbidity conditions (hypertension, diabetes, dyslipidaemia, COPD, hearth failure, renal failure, neoplasms, cardiovascular diseases, inflammatory bowel disease, chronic liver diseases, chronic neurological diseases, autoimmune diseases, endocrine and metabolic diseases). The proportion of ASD patients with a co-occurring psychiatric diagnosis was estimated searching for psychiatric diagnoses (ICD X code: F00 to F99, F84 excluded, and their ICD 9 conversion according to the database encoding) in the AHD-ATS databases; we assumed that the psychiatric conditions persisted over time after the first psychiatric diagnoses were recorded.

As outcome, we investigated consumption in outpatients services (neuropsychiatric, neurologic and neuropsychiatric visits; rehabilitation, test and psychological services), ED admissions, rehabilitation

interventions, territorial-based psychiatry intervention, hospital admissions (psychiatry and neuropsychiatric hospitalisation), residential services, CSS utilisations.

With regard to neuroleptic drugs consumption, we investigated the percentages of ASD patients who have at least one prescription of all psychotropic substances according to the anatomical therapeutic chemical (ATC) classification. We selected all substances with ATC code "N" (nervous system) excluding anaesthetics (N01) and analgesics (NO2). In addition, we investigated antidepressants (N06A), antipsychotic (N05), anxiolytics/tranquilliser (N05B, N05CD, N05CF), ADHD medication (N06BA), and antiepileptic (N03A) as separated groups. Risperidone (N05AX08), Aripiprazole (N05AX12), and valproic acid (N03AX09) consumption were also considered. Frequencies distribution were compared by a chi-squared test.

The binary responses of co-occurring diseases, other psychiatric diagnoses, service consumptions and outcomes at age 16-20 were modelled by repeated measurements using a generalised estimating equation (GEE) approach with a dichotomic response variable. The binary responses for individual ASD patients were assumed to be equally correlated, so an exchangeable correlation structure was assumed; ages were modelled first as a categorical variable with age 18 as reference. Regressions for co-occurring diseases and other psychiatric diagnoses were adjusted by a gender and deprivation index; in addition, logistic regressions for service consumptions and outcomes were adjusted also for co-occurring disease and other psychiatric diagnoses.

Patient and public involvement

Patients and/or public were not involved in the design or conduct this study.

RESULTS

In the period between 2010 and 2017, we identified 5,607 patients, 4,109 male and 1,498 female who met the inclusion criteria. Mean age as at 2017 was 22 years, 19 years old for male and 30 years for female. Prevalence at 8 years old as at 31/12/2017 was 5.4/1,000 inhabitants (95% CI 4.6-6.2); prevalence of male was about three times than in woman: 8.1/1,000 (95% CI 6.8-9.5) for males and 2.6/1,000 inhabitants (95 % CI 1.8-3.5) for females. The incidence rate 2-8 years in 2017 was 2.1 per 1,000 inhabitants/year (95% CI 1.9-2.3). Incidence in males was higher than in females: 3.3 (95% CI 1.9-2.3) for males and 0.8 per 1,000 inhabitants/year (95% CI 0.6-0.9).

We recruited 331 patients who were 18 years old between 2012 and 2015 (Table 1), of whom 257 (77.64%) were male and 74 (22.36%) were female. The gender distribution by calendar year showed a less presence of ADS female in 2012 (p-value 0.03). At 18 years of age, 11.18% were in the less deprived quintile while 20.24% are in the more deprived quintile, any differences were found in the quintile distribution by calendar year (p-value 0.2).

Co-occurring conditions (Table 2) were about 22% at 16 years of age and remained constant among ages (p-value 0.7) as epilepsy (p-value 0.8); no differences were found for the gender (p-value 0.5) and deprivation index. On the contrary, other psychiatric diagnoses increased from 42.6% at 16 years of age to 66.5% at 18 (p-value <0.001), females had a greater risk than males (p-value 0.003) and no differences were found for the deprivation index.

The most reported psychiatric condition was mental retardation (F70-F79), over 30%; schizophrenia, schizotypal and delusional disorders (F20-F29) over 20%; anxiety, dissociative, stress-related, somatoform and other nonpsychotic mental disorders (F40-F48) about 20%. Behavioural and emotional disorders F90-F98 reached 15.4%.

Schizotypal and delusional disorders increased from 11.2% at 16 years old to 26.3% at 18 (p-value 0.001); at 16 years old about 30% of ASD had intellectual disabilities, and that percentage increased with age reaching 39% at 20 (p-value <0.001). We found greater risk for females regarding mood affecting disorders (F30-F39, p-value 0.001) and disorders of adult personality and behaviour (F60-F69, p-value 0.009).

The percentage of ASD patient with at least one health services utilization by age where reported in Table 3. Global access to health and social services decrease both before and after aged 18 (Table 3), with comparable level at 16 and 20 years of age (p-value 0.08).

The percentage of patients receiving a neuropsychiatric visit in outpatient services (Table 3) decreases after 18 years of age (from 30.8% at 18 to 5.4 at 20, OR=0.12; 95% CI 0.07-0.32). On the contrary, neurologist visits increase after 18 years of age (4.9% at 18 to 10.6% at 20, OR=2.52; 95% CI 1.45-4.38) even if only at 20 years of age they reach a statistical significance compared to 18. Psychiatric outpatient services remained stable across all ages (about 14%, no statistically significant difference between ages was found). Psychological (from 15.1% to 3.3%, OR_{20vs18}=0.25; 95%CI 0.13-0.48), rehabilitative (from 19.9% to 3.9%, OR_{20vs18}=0.19; 95%CI 0.11-0.34) and tests (from 6.6% to 1.8%, OR_{20vs18}=0.20; 95%CI 0.08-0.46) care processes provided as outpatient services showed a statistically significant decrease after 18 years of age. The ED rate decreased after 18 years of age, even if it did not reach a statistical significance. The ED admission figure showed a not statistically relevant increase from 16 years of age (19.3%, OR_{16vs18} 0.91 95%CI 0.64-1.28) to 18 (23.3%) and then decreased to 19% (OR_{20vs18}=0.72; 95%CI 0.52-1.01) at age 20.

As territorial-based psychiatry services usually take care of adult patients, the access to this service was investigated starting from 18 years of age. No access before 18 was recorded regarding psychiatry services care and a suggested increase in the utilisation rate was found over 18 (from 15.1% to 20.8, OR_{20vs18} 1.33 95%CI 0.99-1.78) although it did not reach a statistical significance. Considering psychiatric visits both in outpatient services

and territorial care services, a rate increase was observed after 18 years of age, from 17.8% aged 18 to 25.4% 20 (OR=1.48; 95% CI 1.08-2.02). The utilisation of rehabilitation services decreased with age, going from 17.8% to 1.8% (OR_{20vs18}=0.38; 95%CI 0.25-0.59).

Global hospital admission decreased with age, with a significant increase at 17 years of age compared to 18 (from 22.4% to 16.9%, OR=1.80; 95%CI 1.25-2.59). Neuropsychiatric hospital admission and psychiatric hospital admission showed opposite trends, neuropsychiatric ones decreased with age (from 8.8% to 0.3%, OR_{20vs18}=0.06; 95%CI 0.01-0.38) while psychiatric ones increased (from 1.2% to 6.3%, OR_{20vs18}=0.97; 95%CI 0.54-1.74), even if the latter did not reach a statistical significance. It should be noted that neuropsychiatric and psychiatric hospital admissions together remained stable across ages (9.4% at 16 to 6.6% at 20, OR_{20vs18}=0.59; 95%CI 0.35-1.01). The utilisation of residential and semi-residential services was constant across ages (from 6.6% to 6.0%, OR_{20vs18}=0.66; 95%CI 0.43-1.01).

Over than 40% of ASD patients had antipsychotics drug prescriptions, and the percentage increased, even without being statistically significant, with age. Antipsychotics (about 30%) and antiepileptics (about 20%) were the most prescribed drugs and the percentage did not show a statistically significant increase with age. In detail, risperidone (15%) and aripiprazole (from 5% to 10.5) were the antipsychotic drugs most frequently prescribed.

Valproic acid was the most frequent prescription in epileptic drugs (about 20% of ASD patients) and no statistically significant differences were found across ages. Nor any significant differences were found neither by gender nor by deprivation index.

DISCUSSION

Autism is among the most considerable public health problems and between the diagnosis and the age of 18, the Italian healthcare system provides an efficient management model based on child neuropsychiatry.

The results from this study, based on the innovative and integrated use of healthcare and social databases, show that, however, in the transition to adult age, there is a change in the models for taking care of a child diagnosed with autism.

The use of administrative databases allowed us to study real-word diagnostic patterns of a large and unselected population. However, the diagnoses in this analysis were made by physicians specialised in a variety of disciplines, which may lead to a diagnostic imprecision. Indeed, the estimated prevalence at 8 years old (0.54%) is lower than the autism prevalence of 1.68% reported by the most recent study [20]. Nevertheless, our estimation is very close to a value estimated in less recent years [18,36,37] and are similar to the prevalence estimated from administrative

databases in Germany during 2012 [38] for age groups ranging from 6 to 11 years old (0.6%) and in France 0.35% from register based data [39]. In Italy, few studies reporting autism prevalence have been carried out; in a recent paper, Narzisi [40] estimated a prevalence of 0.8% in 7-9 year olds. This figure is higher than ours, but the different study setting might have influenced the results, as Narzisi based the study on a sample at the community level. However, if we considered only children included in Narzisi et al. with both certified disability and ASD, a prevalence of 0.65% would be assessed and this is much closer to our estimate. Since ASD is generally diagnosed after 1 year of age and our administrative data started from 2010, we believe that only a small part of ASD diagnosed patients being 8 years old in 2017 was not included. Our underestimation of ASD may be due to a number of reasons: 1) a delay of diagnosis after 8 years old, 2) a lack of recorded diagnosis in administrative databases, 3) a limited tendency to register the autism diagnosis in Lombardia by physicians; 4) a misclassification diagnosis or 5) only more serious cases were diagnosed by physicians of the NHS.

With respect to incidence, we estimated for 2017 an annual incident rate of about 2/1000 from children aged 2-8, but we were able to find only one study for comparison [18], which estimated an annual incidence of 1.02/1000 in boys and 0.21/1000 in girls aged 2-8. This figure is lower than ours, however it is referred to 2010, and the incidence of ASD in these years could have increased. Furthermore, we were able to estimate an incidence for children 2-6 years old between 2015 and 2017 and we estimated (data not shown) 4.30/1000 for 2015, 4.70 for 2016 and 7.30 for 2017. This suggested and increasing trend for ASD diagnoses that will be reflected on the prevalence of the following years.

Our study investigated the differences in rates of comorbidity and healthcare services utilisation in a selected retrospective longitudinal cohort of ASD patients from 16 to 20 years old.

Giving that fact, the recruited ASD cohort included selected ASD subjects who had been recruited as patients with health/social care services utilisation over seven years (from 2010 to 2017). Thus, the finding in that cohort could not be connected to general ASD patients during the transition age but to ASD patients who were included in a health/social services pathway and, perhaps, with more serious conditions. In that view, our findings of a high rate (up to 66.5%) of psychiatric conditions (including mental retardation) were not completely surprising, even if higher than those reported in other studies (34%[41], 54% [7], 65% [37]). In detail, the percentage of anxiety previously reported [41] was similar (14.4%) to ours (19.3%), as well as depression (9.9 vs 13.3). The percentage of epilepsy (9%) is comparable with other studies about the transition age in ASD [41].

In Italy, patients remain in charge of paediatric healthcare services until 18 years old, however starting from 16 years of age some overlapping in healthcare assignment may occur. The results of this study suggest that the type

of medical services used for ASD patients changes at an age between 16 to 20 years old. Although comparison between ages showed that general healthcare services utilisation increases from 16 to 18 years old and subsequently decreases.

It is possible that ADS patients in transitional age were no longer assisted by neuropsychiatric or rehabilitation services and they stated to be assisted by psychiatric and CSS with other diagnoses. Neuropsychiatric and Rehabilitation services decreased with age while ASD patients started to be treated by territorial psychiatric services and CSS, this suggested a change in a care path for these people. Indeed, the percentage of ASD patients with at least one psychiatric territorial-based treatment increased from 18 to 20 years of age. Even the percentage of ASD patients having psychiatric visit at least in outpatient care services or territorial care services increased from 12.7% at 16 years old to 25.4 at 20 years old. This change in patients' reference services was also confirmed by the decreased rate of ASD patient with neuropsychiatric hospitalisation and the corresponding increase of psychiatric hospitalisation, even if globally the hospitalisation in dedicated departments (neuropsychiatric or psychiatric) remained stable across ages. This suggested that ASD patients and their families might look for new therapeutic references around the 18th year and then settle down, even if a long-time observation may be necessary. In conclusion, we did not observe a decrease in healthcare services utilisation as recently reported by Nathenson et al [42].

The percentage of ASD people who received at least one service related to an ED remains stable with age, although a slight increase in 17-19 olds was observed. This suggests that even if the therapeutic references may have changed with age, this did not imply a greater need of the ED.

Even if the current evidence for the effectiveness of antipsychotics drugs in ASD is only moderate [8], neuroleptic drugs were frequently used in this cohort of ASD patients and their consumption remained stable across ages; moreover, our findings were similar to frequencies reported in other studies [37]. ADHD drugs were less prescribed (less than 0.6%) with respect to other reported prescription rates in ASD patients (about 15%) even considering the patients' age [43], this may reflect a generally low consumption in Italy of such drugs in childhood [44].

Strengths and Limitations

The current study used large administrative databases, which made it possible to study real-word diagnostic patterns of a large and unselected population, without non-responses, interviews or recall bias issues. However, we must note that we could not include any service utilisation outside the NHS. Furthermore, diagnoses in administrative databases are made by physicians specialised in a variety of disciplines and were not validated,

which may lead to diagnostic imprecision. In addition, some diagnoses may not have been reported. Speaking about the estimated rate of ASD patients who used healthcare services, we investigated what type of diagnosis these outcomes were associated with and which were the reasons for such services. Besides, the CSS and Rehabilitation interventions database did not systematically report the type of services provided (i.e. speech therapy, rehabilitation, occupational therapy). As co-occurring conditions, we could include only selected items from the Co-payment Exemption Register and psychiatric conditions were reported in the general category.

The 16-20 age range provides an opportunity to investigate ASD patients during the transition from paediatric toward to young adult services and we were able to follow longitudinally a selected group of ASD patients in transition age without the birth cohort effect. Unfortunately, our cohort was limited to adolescents with ASD who had had at least one healthcare service consumption with a diagnosis code related to ASD starting from 2010, so ASD patients who did not use healthcare services during this period would not be included. Accordingly, our findings may not be applied to all ASD patients in transition age but represented ASD patients with some healthcare service connection.

Our study suggested a change in the "therapeutic references" but we did not find a reduction in the use of healthcare services with age. However, we were not able to include a survey on caregivers in order to investigate the actual difficulty in managing this transition. Moreover, psychiatric healthcare services may not be the proper type of support considering the special needs (such as speech therapy, rehabilitations, occupational therapy) of these patients.

CONCLUSION

Our finding suggested that ASD patients changed "therapeutic references" with age from neuropsychiatric and rehabilitative services towards psychiatric and community-based services. The rising in prevalence of ASD in children means there will be a large numbers of ADS adolescents that will be entering the young adult's healthcare system in the future. This fact should be taken in account when planning future public healthcare policies and interventions.

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Contributors: ST, AGR, and MB conceived and devised the study, and ST analysed the data. All authors contributed to the interpretation of the data. ST drafted the article and all authors (AGR and MB) reviewed and edited the manuscript, and approved the version to be published, and agree to be accountable for all aspects of the work. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. ST and AGR accept full responsibility for the work and the conduct of the study, had access to the data, and controlled the decision to publish.

Compliance with Ethical Standards : The data are administrative ones, so no informed consent was necessary.

Competing interests: The research being reported in this publication was supported by Roche. The funder had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. The author reports no other conflicts of interest in this work.

Data sharing statement: The administrative data used for the present study contain sensitive information of underage people. Even though data have been anonymised we will not be able to share your data with other researchers.

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Table 1. Demographics characteristic of ADS patients at 18th years old

Calendar years of recruitment	ADS patient	Gender		Quintile of Deprivation Index				
	N. (%)	*Female* % (N.)	*Male* % (N.)	*I* more rich	*II*	*III*	*IV*	*V* more poor
2012	69 (20.85%)	20.29% (14)	79.71% (55)	11.59% (8)	15.94% (11)	23.19% (16)	27.54% (19)	20.29% (14)
2013	75 (22.66%)	12.00% (9)	88.00% (66)	5.33% (4)	24.00% (18)	17.33% (13)	28.00% (21)	25.33% (19)
2014	92 (27.79%)	31.52% (29)	68.48% (63)	16.30% (15)	18.48% (17)	25.00% (23)	27.17% (25)	11.96% (11)
2015	95 (28.70%)	23.16% (22)	76.84% (73)	10.53% (10)	22.11% (21)	22.11% (21)	20.00% (19)	24.21% (23)
All	331	22.36% (74)	77.64% (257)	11.18% (37)	20.24% (67)	22.05% (73)	25.38% (84)	20.24% (67)

Table 2. Distribution of other psychiatric diagnosis and co-occurring condition by age and regression model output

	Age (years) % (N.)					Age as categorical OR (95%CI)					Age as continuous OR (95%CI)	
Conditions	**16**	**17**	**18**	**19**	**20**	**Female vs Male**	**17 vs 16**	**18 vs 16**	**19 vs 16**	**20 vs 16**	**Female vs Male**	**Age effect**
All epilepsy included	22.4% (74)	20.2% (67)	21.8% (72)	20.8% (69)	21.8% (72)	0.86 (0.51-1.45)	1.04 (0.83-1.29)	0.91 (0.76-1.10)	0.97 (0.79-1.19)	0.98 (0.79-1.22)	0.89 (0.53-1.50)	0.99 (0.93-1.05)
Epilepsy	9.1% (30)	8.2% (27)	10.3% (34)	10% (33)	9.7% (32)	0.92 (0.45-1.90)	0.87 (0.65-1.16)	0.78 (0.61-0.98)	0.92 (0.71-1.20)	0.90 (0.71-1.15)	1.01 (0.49-2.08)	1.01 (0.93-1.10)
Psychiatric diagnosis	42.6% (141)	50.8% (168)	59.8% (198)	63.7% (211)	66.5% (220)	2.06 (1.27-3.33)	0.48 (0.41-0.58)	0.68 (0.60-0.77)	1.17 (1.01-1.36)	1.36 (1.20-1.53)	2.08 (1.29-3.36)	1.30 (1.23-1.37)
F00-F09	0.9% (3)	1.8% (6)	3.3% (11)	4.2% (14)	4.8% (16)	1.68 (0.53-5.26)	0.26 (0.10-0.70)	0.53 (0.31-0.92)	1.21 (0.97-1.51)	1.48 (1.05-2.09)	1.82 (0.60-5.54)	1.41 (1.21-1.64)
F20-F29	11.2% (37)	16.9% (56)	20.8% (69)	23.9% (79)	26.3% (87)	1.37 (0.77-2.44)	0.47 (0.36-0.61)	0.77 (0.67-0.88)	1.07 (1.01-1.13)	1.37 (1.19-1.57)	1.33 (0.75-2.35)	1.27 (1.20-1.36)
F30-F39	2.7% (9)	6.3% (21)	8.5% (8)	10.6% (35)	13.3% (44)	3.25 (1.62-6.50)	0.29 (0.17-0.51)	0.72 (0.57-0.91)	1.23 (1.02-1.48)	1.69 (1.32-2.16)	3.14 (1.61-6.14)	1.43 (1.30-1.59)
F40-F48	6.9% (23)	10.6% (35)	13.6% (45)	16.9% (56)	19.3% (64)	1.46 (0.77-2.78)	0.48 (0.35-0.65)	0.74 (0.62-0.89)	1.31 (1.12-1.53)	1.55 (1.28-1.88)	1.44 (0.76-2.72)	1.31 (1.21-1.42)
F60-F69	5.7% (19)	9.1% (30)	13.3% (44)	16.9% (56)	18.7% (62)	2.28 (1.23-4.25)	0.39 (0.26-0.57)	0.64 (0.51-0.80)	1.34 (1.14-1.58)	1.53 (1.26-1.84)	2.14 (1.16-3.94)	1.35 (1.25-1.47)
F70-F79	26.9% (89)	29.9% (99)	35% (116)	37.2% (123)	39% (129)	1.52 (0.92-2.52)	0.68 (0.59-0.78)	0.79 (0.71-0.88)	1.10 (1.01-1.19)	1.19 (1.08-1.30)	1.52 (0.92-2.51)	1.15 (1.10-1.20)
F90-F98	10.6% (35)	11.2% (37)	12.7% (42)	14.2% (47)	15.4% (51)	1.01 (0.48-2.11)	0.81 (0.70-0.95)	0.86 (0.76-0.98)	1.11 (1.00-1.24)	1.23 (1.07-1.41)	1.01 (0.49-2.12)	1.11 (1.05-1.17)

Table 3. Analysis of the access to health / social services in ASD patients and Odds ratio (OR) and corresponding confidence intervals from logistic regression

	Age (years) % (N.)						Age as categorical OR (95%CI)				Age as continuous OR (95%CI)	
	16	17	18	19	20	Female vs Male	17 vs 16	18 vs 16	19 vs 16	20 vs 16	Female vs Male	Age effect
Visit NPI	15.4% (51)	25.1% (83)	30.8% (102)	10% (33)	5.4% (18)	1.19 (0.77-1.85)	0.47 0.34-0.67)	0.79 (0.59-1.07)		0.12 (0.07-0.20)	1.15 (0.76-1.74)	0.76 (0.69-0.84)
Visit Neurology	4.5% (15)	3.3% (11)	4.8% (16)	6.6% (22)	10.6% (35)	1.66 (0.87-3.19)	1.11 (0.55-2.22)	0.78 (0.38-1.60)		2.52 (1.45-4.38)	1.68 (0.87-3.22)	1.29 (1.10-1.53)
Visit Psychiatry	12.7% (42)	10% (33)	13.6% (45)	13.6% (45)	14.8% (49)	0.95 (0.64-1.41)	0.97 (0.62-1.50)	0.75 (0.48-1.19)		1.07 (0.70-1.64)	0.94 (0.64-1.40)	1.05 (0.94-1.17)
Outpatient test	6.6% (22)	6.6% (22)	8.5% (28)	3% (10)	1.8% (6)	1.05 (0.59-1.87)	0.78 (0.42-1.46)	0.78 (0.45-1.33)		0.2 (0.08-0.46)	1.06 (0.60-1.87)	0.76 (0.65-0.87)
Outpatient rehabilitation	19.9% (66)	20.2% (67)	16.9% (56)	3.9% (13)	3.9% (13)	1.09 (0.65-1.83)	1.38 (0.97-1.96)	1.33 (0.99-1.79)	0.2 (0.11-0.35)	0.19 (0.11-0.34)	1.09 (0.65-1.81)	0.62 (0.56-0.69)
Psychological support	15.1% (50)	13.3% (44)	12.1% (40)	6.3% (21)	3.3% (11)	1.74 (1.02-2.98)	1.37 (0.95-1.98)	1.18 (0.81-1.7)	0.4 (0.3-0.73)	0.25 (0.13-0.48)	1.74 (1.02-2.98)	1.37 (0.95-1.98)
Emergency room access	19.3% (64)	22.7% (75)	23.3% (77)	21.5% (71)	19% (63)	1.22 (0.82-1.81)	0.91 (0.64-1.28)	1.03 (0.73-1.44)	0.86 (0.62-1.20)	0.72 (0.51-1.01)	1.22 (0.82-1.81)	0.94 (0.86-1.02)
Psychiatry access	0% (0)	0.9% (3)	15.1% (50)	19.3% (64)	20.8% (69)	0.9 (0.5-1.63)	-	-	1.27 (0.97-1.66)	1.33 (0.99-1.78)	0.88 (0.49-1.6)	1.15 (0.99-1.32)
Rehabilitation access	17.8% (59)	13.3% (44)	11.5% (38)	4.8% (16)	1.8% (6)	1.33 (0.73-2.43)	1.77 (1.35-2.33)	1.22 (1.02-1.45)	0.38 (0.25-0.59)	0.14 (0.06-0.30)	1.43 (0.79-2.59)	0.61 (0.54-0.68)
Psychiatry visits and access	12.7% (42)	10.3% (34)	17.8% (59)	23.6% (78)	25.4% (84)	1 (0.66-1.52)	0.78 (0.52-1.16)	0.57 (0.37-0.86)	1.39 (1.02-1.9)	1.48 (1.08-2.02)	0.99 (0.65-1.5)	1.22 (1.11-1.35)
Hospital admission	16.9% (56)	22.4% (74)	16.9% (56)	19.3% (64)	16% (53)	1.12 (0.75-1.66)	1.42 (0.98-2.05)	1.80 (1.25-2.59)	1.11 (0.78-1.59)	0.82 (0.54-1.23)	1.12 (0.75-1.66)	0.86 (0.78-0.94)

psychiatry	1.2% (4)	2.7% (9)	5.7% (19)	8.5% (28)	6.3% (21)	1.24 (0.68-2.28)	0.29 (0.1-0.79)	0.54 (0.26-1.12)	1.44 (0.89-2.33)	0.97 (0.54-1.74)	1.26 (0.69-2.29)	1.28 (1.1-1.49)
NPI	8.8% (29)	10.3% (34)	4.5% (15)	0.9% (3)	0.3% (1)	1.89 (0.97-3.7)	3.18 (1.77-5.72)	3.19 (1.84-5.52)	0.18 (0.02-1.4)	0.06 (0.01-0.38)	1.96 (1-3.84)	0.44 (0.38-0.51)
Psychiatry+NPI	9.4% (31)	10.6% (35)	9.4% (31)	9.4% (31)	6.6% (22)	1.40 (0.85-2.31)	1.48 (0.92-2.40)	1.43 (0.92-2.22)	0.77 (0.47-1.27)	0.59 (0.35-1.01)	1.41 (0.86-2.32)	0.80 (0.7-0.91)
residencial services	6.6% (22)	6.3% (21)	8.8% (29)	7.3% (24)	6% (20)	0.97 (0.45-2.05)	0.82 (0.52-1.30)	0.76 (0.53-1.10)	0.82 (0.52-1.30)	0.66 (0.43-1.01)	1.00 (0.47-2.13)	0.95 (0.81-1.10)
Social access	4.8% (9)[a]	11.1% (29)[a]	18.4% (61)	20.5% (68)	21.8% (72)	1.46 (0.78-2.74)	0.20 (0.1-0.41)	0.51 (0.37-0.7)	1.33 (0.97-1.82)	1.21 (1.02-1.45)	1.49 (0.81-2.73)	1.33 (1.22-1.45)
All access	46.5% (154)	58.6% (194)	68% (225)	57.4% (190)	54.1% (179)	1.40 (0.95-2.07)	0.47 (0.35-0.64)	0.73 (0.56-0.96)	0.72 (0.54-0.96)	0.44 (0.33-0.59)	1.36 (0.92-2)	0.97 (0.9-1.06)

[a] Since databases started from 2012 as denominator we included only contributing age after 2012

(Cont'd)

Table 3. (Continue) Analysis of the access to health / social services in ASD patients and Odds ratio (OR) and corresponding confidence intervals from logistic regression

	Age (years) % (N.)						Age as categorical OR (95%CI)					Age as continuous OR (95%CI)
	16	17	18	19	20	Female vs Male	17 vs 16	18 vs 16	19 vs 16	20 vs 16	Female vs Male	Age effect
Neurolepctic prescriptions	20.2% (67)	21.8% (72)	23.6% (78)	25.4% (84)	24.2% (80)	0.82 (0.49-1.36)	1.14 (0.86-1.52)	1.09 (0.87-1.36)	1.08 (0.86-1.36)	0.97 (0.76-1.23)	0.81 (0.48-1.34)	0.96 (0.89-1.04)
risperidone	15.7% (52)	15.4% (51)	15.7% (52)	15.4% (51)	15.4% (51)	0.54 (0.31-0.94)	1.32 (0.97-1.80)	1.15 (0.89-1.48)	0.99 (0.77-1.27)	0.90 (0.67-1.20)	0.54 (0.31-0.94)	0.91 (0.83-0.99)
aripiprazole	5.1% (17)	8.5% (28)	10.3% (34)	11.5% (38)	10.9% (36)	1.47 (0.74-2.92)	0.66 (0.40-1.08)	0.99 (0.70-1.40)	1.11 (0.80-1.56)	1.04 (0.73-1.50)	1.47 (0.73-2.94)	1.09 (0.97-1.24)
atomoxetine	0.3% (1)	0.3% (1)	0.3% (1)	0% (0)	0.3% (1)							
methylphenidate	0.3% (1)	0.3% (1)	0.3% (1)	0% (0)	0.3% (1)							
All neurological prescriptions	35.6% (118)	39.3% (130)	44.7% (148)	45% (149)	44.1% (146)	1.18 (0.74-1.88)	0.91 (0.74-1.14)	0.93 (0.78-1.10)	0.95 (0.78-1.15)	0.85 (0.68-1.07)	1.18 (0.74-1.89)	0.98 (0.92-1.05)
antidepressant	5.7% (19)	7.9% (26)	10.6% (35)	9.4% (31)	11.2% (37)	2.54 (1.40-4.64)	0.63 (0.40-0.98)	0.78 (0.54-1.15)	0.83 (0.58-1.19)	0.99 (0.66-1.50)	2.50 (1.37-4.55)	1.10 (0.98-1.24)
Psychiatric prescriptions	27.8% (92)	30.8% (102)	33.8% (112)	34.1% (113)	34.7% (115)	0.57 (0.34-0.96)	1.04 (0.72-1.49)	1.01 (0.75-1.36)	0.99 (0.73-1.34)	0.91 (0.65-1.27)	0.57 (0.34-0.96)	0.97 (0.87-1.07)
anxiolytic	0.9% (3)	1.8% (6)	1.5% (5)	1.5% (5)	1.5% (5)	3.63 (0.84-15.61)	0.70 (0.24-2.04)	1.48 (0.76-2.85)	0.99 (0.51-1.92)	1.06 (0.43-2.66)	6.00 (1.37-26.24)	1.06 (0.80-1.41)
antiepileptic	16.3% (54)	16.3% (54)	20.8% (69)	23.0% (76)	23.9% (79)	1.22 (0.71-2.08)	0.91 (0.72-1.16)	0.84 (0.68-1.03)	1.11 (0.92-1.34)	1.13 (0.90-1.41)	1.22 (0.72-2.08)	1.06 (0.99-1.13)
valproic acid	12.7% (42)	10.9% (36)	15.4% (51)	16.3% (54)	18.1% (60)	1.02 (0.54-1.92)	1.01 (0.77-1.33)	0.77 (0.58-1.02)	1.04 (0.84-1.30)	1.15 (0.88-1.49)	1.02 (0.55-1.88)	1.04 (0.96-1.13)
AHDH prescriptions	0.6% (2)	0.6% (2)	0.6% (2)	0% (0)	0.3% (1)							

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DO AUTISTIC PATIENTS CHANGE HEALTHCARE SERVICES UTILISATION THROUGH THE TRANSITION-AGE? A LONGITUDINAL RETROSPECTIVE STUDY

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DO AUTISTIC PATIENTS CHANGE HEALTHCARE SERVICES UTILISATION THROUGH THE TRANSITION-AGE? A LONGITUDINAL RETROSPECTIVE STUDY

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DO AUTISTIC PATIENTS CHANGE HEALTHCARE SERVICES UTILISATION THROUGH THE TRANSITION-AGE? A LONGITUDINAL RETROSPECTIVE STUDY

ABSTRACT

Objectives: The purpose of this paper is to provide an estimate of the prevalence rate of autism spectrum disorder (ASD) at 8 years of age in 2017 based on administrative databases and to investigate the change in healthcare services use during the transition-age.

Design: Longitudinal retrospective cohort study

Setting: Administrative Healthcare Database (2010-2017) in Italy

Participants: We identified 5,607 ASD patients; 331 ASD patients from 2012 to 2015 in the calendar year of their 18th birthday were selected and their health service utilisation during a 5-year period - the two years preceding and succeeding their 18th year - were investigated.

Interventions: none

Primary and secondary outcome measures: Prevalence, incidence, and proportion of ASD patients receiving specific healthcare services

Results: Prevalence of ASD at age 8 was 5.4/1,000. Global access to health and social services was lower both before and after age 18 (46.5% at 16, 68% at 18, 54.1% at 20). The percentage of patients receiving a neuropsychiatric consultation decreased after age 18 (30.8% at 18, 5.4% at 20). Community mental health services (CMHS) utilisation rate increased above 18 years of age. Regarding psychiatric visits, for both outpatient and CMHS services, an increase was observed from 17.8% at age 18 to 25.4% at age 20. The utilisation of rehabilitation services decreased with age, going from 17.8% at age 16 to 1.8% at age 20. Psychiatric outpatient services remained stable across ages at about 14%.

Conclusions: Our findings suggest that ASD patients changed “therapeutic references” with age from neuropsychiatric and rehabilitative services towards psychiatric and community-based services as they transitioned from paediatric to young adult’s healthcare services.

Keywords: Autism spectrum disorder; Epidemiology; Administrative databases; Health outcomes; Health service research

Strengths and limitations of this study

- Longitudinal retrospective cohort study based on Administrative Healthcare Database: real-world diagnostic patterns of a large and unselected population (3.5 million habitants)
- Estimation of prevalence and incidence rates, differences in comorbidity, and healthcare services utilisation in an unselected retrospective longitudinal cohort of ASD patients from 16 to 20 years of age
- Diagnosis codes and healthcare services utilisation were based only on the administrative data

INTRODUCTION

Autism spectrum disorder (ASD) is a brain-based chronic neurodevelopmental disorder with lifelong impacts. It is characterised and diagnosed by impairments in social communication and social interaction with the presence of restricted, repetitive behaviours [1]. Onset of ASD typically occurs by age 3, although some studies suggest that symptoms can emerge between 6 and 18 months of age and may not be fully manifested until school age [2,3]. Children, adolescents, and adults with ASD can often present a number of comorbidities including psychiatric conditions, intellectual disabilities, developmental delay, epilepsy, anxiety, language and motor difficulties, and depression [4–7].

The aetiology of ASD remains largely unexplained. It seems to be highly heritable [8] and some environmental risk factors [9] and parental age [10] may be involved [11]. The prevalence of ASD has increased in the last decades, although the reasons for this increase are not fully understood. It might be related to etiologic, non-etiologic, and administrative factors (e.g. modified diagnostic criteria, improved access to services, and increased public and scientific interest [6,12,13]).

A review published in 2012 [14] estimated the global prevalence of ASD to be about 1% (62/10000); a more recent study has estimated the prevalence to be 1.5% in developed countries [11,15,16]. In 2014 [15], a prevalence rate of 16.8 per 1000 was estimated for children aged 8.

Treatments for ASD vary across the world and even within country regions and it has been reported that parents with a lower educational level are less successful in obtaining specialist interventions that could improve outcomes [6]. Treatments for ASD include early parent-mediated interventions and behavioural and social treatments. Evidence-based pharmacology in ASD is currently limited to the treatment of co-occurring behaviours or diagnoses and not ASD itself [6]. Risperidone [17] and aripiprazole [18] have improved

symptoms of irritability or agitation in children and adolescents with ASD. Methylphenidate [19], atomoxetine [20], and guanfacine [21] have shown a benefit for ADHD symptoms in ASD. However, the use of such drugs presents some adverse effects and their use has been indicated during a specific age period.

While autism is generally considered a disorder of childhood, the rise in ASD prevalence in the last decades has produced an increase of individuals with ASD transitioning from paediatric to young adult medical services resulting in autism rapidly becoming a disorder of adulthood as well [22]. There is evidence that for young people with special healthcare needs, such as autism, transitioning form paediatric to adult healthcare represents a problem [23,24]. The transition process may be especially difficult for young people whose special healthcare needs involve mental health, developmental disabilities, or intellectual disabilities [24]. Moreover, the lack of ASD treatment guidelines for adult patients increases the complexity of healthcare delivery and involves a problematic transition from paediatric to adult healthcare [25]. Very often, the transition to adulthood in people with ASD results in poor outcomes across multiple domains including employment, education, healthcare, social engagement, and independent living [26,27], even in the presence of healthcare transition services [28]. This may represent problems both for parents [27] and patients [29].

Often the transition from the paediatric to adult healthcare system coincides with an exit from the educational system (i.e. high school) where adolescents may receive daily support that may further affect service usage. However, to our knowledge, only a few studies have described changes in healthcare service usage during the transition to adulthood in people with ASD [24,26,30]. Administrative claims data can be plentiful, comprehensive, cost efficient, and free from some of the biases that accompany other types of data, such as surveys or self-reports [31]. Analyses of administrative healthcare databases have the potential to include a large number of individuals and have been successfully used in the study of health outcomes associated with a

variety of conditions [31,32]. Studies conducted in the US [33] and Canada [34,35] have indicated that administrative claims data were able to clearly identify children with ASD.

The purpose of this paper is to provide an estimate of the prevalence of ASD at 8 years of age using administrative databases derived from the largest Northern Italian population. Further, this study investigated the change in healthcare services use during the transition from the paediatric to young adult healthcare systems.

METHODS

Data collection

A retrospective cohort study was conducted using the Administrative Healthcare Database of the Agency for Health Protection of Milan (AHD-ATS) from January 1, 2010 to December 31, 2017. Only data regarding patients residing in the ATS were considered. In Italy, the National Healthcare System (NHS) is universal and fully covers the population and the ATS provides care to about 3,500,000 inhabitants.

Data were obtained from AHD-ATS, which included 8 different databases: 1) outpatient activity data (6 million (M) records), such as visits and tests performed by residents in the study area in ambulatories and laboratories; 2) hospital discharge records (1M); 3) co-payment Exemption Register (1M); 4) emergency department (ED) visits (2M); 5) rehabilitation interventions database (800,000), such as visits and rehabilitative therapy (i.e. speech therapy, physiotherapy, and educative and occupational therapy); 6) community mental health services (CMHS) (100,000) such as psychiatry visits, residential facilities, pharmacological interventions, and family support in psychiatric setting; 7) pharmaceutical prescription database (200M); and 8) community and social services (CSS) (1M) such as family support, day care centres, community and residential facilities, home care, home care economic aid, and hospice.

These databases can be linked through a unique identifier code; demographic information was obtained by record linkage using a unique identifier code with patients' master

data and Deprivation Index by using record linkage with the 2001 General Census of Population and Housing.

ASD patients were defined as individuals having a reported diagnosis of ASD (ICD-9 codes 299.00 to 299.99 or their ICD-10 equivalents) in at least one of the databases during the study period [35]. For each patient, the calendar year of birth was used as an approximate age value at the time of service utilisation.

Statistical analysis

Prevalence and incidence rates estimation

Prevalence rates at age 8 and 2-8 years incidence rates based on administrative databases were estimated for 2017. The prevalence rate was obtained by dividing the number of children 8 years old diagnosed as ASD in 2017 or previously, by the population size – of the same age – in the study area at 1 January 2018 based on the Italian National Institute of Statistics.

The annual incidence rates were obtained by dividing the annual number of children aged 2-8 years newly diagnosed by the general population subtracting the number of ASD diagnoses in preceding years. Binomial 95% confidence intervals (95%CI) were calculated for the prevalence and incidence rates.

Consumptions and outcome models

We selected ASD patients from 2012 to 2015 in the calendar year of their 18th birthday, and we investigated Health Services utilisation during a 5-year period: the two years preceding and succeeding their 18th year as well as the year of their 18th birthday (i.e. aged from 16 to 20). We investigated the percentage of co-occurring conditions related to other psychiatric diseases; as an outcome variable, we investigated access to services (i.e. outpatient, rehabilitation interventions, community/social services, ED access, hospital admissions, and neuroleptic drug consumption).

Co-occurring conditions were identified by using the chronicity database [36] that covers the 13 main comorbidity conditions (hypertension, diabetes, dyslipidaemia, COPD, heart failure, renal failure, neoplasms, cardiovascular diseases, inflammatory bowel disease, chronic liver diseases, chronic neurological diseases, autoimmune diseases, and endocrine and metabolic diseases). The proportion of ASD patients with a co-occurring psychiatric diagnosis was estimated searching for psychiatric diagnoses (ICD-10 code: F00 to F99, F84 (autistic disorder) excluded, and their ICD-9 conversion according to the database encoding) in the AHD-ATS databases; we assumed that the psychiatric conditions persisted over time after the first psychiatric diagnoses were recorded.

As outcomes, we investigated consumption of outpatient services (psychiatric, neurologic, and neuropsychiatric visits; tests and psychological services), ED admissions, rehabilitation interventions, CMHS interventions, hospital admissions (psychiatry and neuropsychiatric hospitalisation), residential services, and CSS utilisations.

With regard to neuroleptic drug consumption, we investigated the percentages of ASD patients who had at least one prescription for any psychotropic substances according to the anatomical therapeutic chemical (ATC) classification. We selected all substances with ATC code "N" (nervous system) excluding anaesthetics (N01) and analgesics (N02). In addition, we included antidepressants (N06A), antipsychotics (N05), anxiolytics/tranquillisers (N05B, N05CD, N05CF), ADHD medication (N06BA), and antiepileptics (N03A) as separate groups. risperidone (N05AX08), aripiprazole (N05AX12), and valproic acid (N03AX09) consumption was also considered.

The binary responses of co-occurring diseases, other psychiatric diagnoses, service consumptions, and outcomes at ages 16-20 were modelled by repeated measurements using a generalised estimating equation (GEE) approach with a dichotomic response variable. The binary responses for individual ASD patients were assumed to be equally correlated, so an

exchangeable correlation structure was assumed; ages were modelled first as a categorical variable with age 18 as reference. Regressions for co-occurring diseases and other psychiatric diagnoses were adjusted by a gender and deprivation index; in addition, logistic regressions for service consumption and outcomes were adjusted for co-occurring diseases and other psychiatric diagnoses.

Patient and public involvement

Neither patients nor the public were involved in the design or conduct of this study. Ethics approval was not required given that ATS has among its institutional functions the evaluation of the care pathways of autistic patients transitioning to adulthood which is considered a critical element to monitor at present in NHS. Patient identity was masked by anonymization according to the standard ISO 25237:201. Their unique identification number (fiscal code) was transcoded into a string by the Information System of ATS, which had no role in analysing the data.

RESULTS

In the period between 2010 and 2017, we identified 5,607 patients (4,109 male and 1,498 female) who met the inclusion criteria. Mean age as at 2017 was 22 years, 19 years old for males and 30 years for females. Based on administrative data, the prevalence of ASD at 8 years old on 31 December 2017 was 5.4/1,000 inhabitants (95%CI 4.6-6.2); prevalence for males was about three times that of females: 8.1/1,000 (95%CI 6.8-9.5) for males and 2.6/1,000 inhabitants (95 % CI 1.8-3.5) for females. The incidence rate for 2-8 years in 2017 was 2.1 per 1,000 inhabitants/year (95%CI 1.9-2.3). Incidence in males was higher than in females: 3.3 (95%CI 1.9-2.3) for males and 0.8 per 1,000 inhabitants/year (95%CI 0.6-0.9) for females.

We selected 331 patients who were 18 years old between 2012 and 2015 (Table 1), of whom 257 (77.64%) were male and 74 (22.36%) were female. With regard to the deprivation index, at 18 years of age, 11.18% were in the least deprived quintile while 20.24% were in the

most deprived quintile; no differences were found in the quintile distribution by calendar year (*p*-value=0.2).

Co-occurring conditions (Table 2) were present in about 22% of patients at 16 years of age and remained constant among ages; no differences were found for gender or deprivation index. In contrast, other psychiatric diagnoses increased from 42.6% at 16 years of age to 66.5% at age 18 (*p*-value <0.001); females had a greater risk than males (*p*-value=0.003) and no differences were found for the deprivation index.

The most reported psychiatric condition was mental retardation (F70-F79) at over 30%; schizophrenia, schizotypal, and delusional disorders (F20-F29) were over 20%; anxiety, dissociative, stress-related, somatoform, and other nonpsychotic mental disorders (F40-F48) were about 20%. Behavioural and emotional disorders F90-F98 reached 15.4%.

Schizotypal and delusional disorders increased from 11.2% at 16 years old to 26.3% at age 18 (*p*-value=0.001); at 16 years old about 30% of individuals with ASD had intellectual disabilities, and that percentage increased with age reaching 39% at 20 years (*p*-value <0.001). We found a greater risk for females regarding mood affecting disorders (F30-F39, *p*-value <0.001) and disorders of adult personality and behaviour (F60-F69, *p*-value=0.009).

The percentage of ASD patients with at least one access to health services by age is reported in Table 3. Global access to health and social services are lower both before and after age 18 (Table 3), with comparable levels at 16 and 20 years of age (*p*-value=0.08).

The percentage of patients receiving a neuropsychiatric consultation (Table 3) decreases after 18 years of age (from 30.8% at age 18 to 5.4% at age 20, OR=0.12; 95%CI 0.07-0.32). However, neurologist visits increase after 18 years of age (4.9% at age 18 to 10.6% at 20, OR=2.52; 95%CI 1.45-4.38) and only at 20 years of age reach statistical significance compared to age 18. Psychiatric outpatient visits remained stable across all ages (14%). Healthcare provided as outpatient services showed a statistically significant decrease after 18 years of age

(i.e. psychological services (from 15.1% at age 18 to 3.3% at age 20, OR_{20vs18}=0.25; 95%CI 0.13-0.48); rehabilitative services (from 19.9% to 3.9%, OR_{20vs18}=0.19; 95%CI 0.11-0.34); and tests (from 6.6% to 1.8%, OR_{20vs18}=0.20; 95%CI 0.08-0.46)). The ED admission figure showed a significant increase from 16 years of age (19.3%) to age 18 (23.3%, OR_{16vs18} 0.91 95%CI 0.64-1.28) and then decreased to 19% (OR_{20vs18}=0.72; 95%CI 0.52-1.01) at age 20.

As CMHS usually take care of adult patients, access to this service was investigated starting from 18 years of age. No access to CMHS was recorded before age 18 and an increase in the utilisation rate was found over age 18 (from 15.1% at age 18 to 20.8% at age 20, OR_{20vs18}=1.33; 95%CI 0.99-1.78). With regard to psychiatric visits both in outpatient services and CMHS, a rate increase was observed after 18 years of age, from 17.8% at age 18 to 25.4% at age 20 (OR_{20vs18}=1.48; 95%CI 1.08-2.02). The utilisation of rehabilitation services decreased with age, going from 17.8% at age 18 to 1.8% at age 20 (OR_{20vs18}=0.38; 95%CI 0.25-0.59).

Global hospital admissions decreased with age, with a significant decrease at 18 years of age compared to age 17 (from 22.4% at age 17 to 16.9% at age 18, OR_{17vs18}=1.80; 95%CI 1.25-2.59). Neuropsychiatric and psychiatric hospital admissions showed opposite trends: neuropsychiatric accesses decreased with age (from 8.8% at age 18 to 0.3% at age 20, OR_{20vs18}=0.06; 95%CI 0.01-0.38) while psychiatric accesses increased (from 1.2% at age 18 to 6.3% at age 20, OR_{20vs18}=0.97; 95%CI 0.54-1.74). It should be noted that neuropsychiatric and psychiatric hospital admissions together remained stable across ages (9.4% at age 16 to 6.6% at age 20, OR_{20vs18}=0.59; 95%CI 0.35-1.01).

More than 40% of ASD patients had neurological drug prescriptions, and the percentage increased with age, although the increase was not statistically significant. Antipsychotics (about 30%) and antiepileptics (about 20%) were the most commonly prescribed drugs and these percentages did not show a statistically significant increase with age. In detail, risperidone (15%) and aripiprazole (from 5% to 11.5%) were the antipsychotic drugs most frequently

prescribed. Valproic acid was the most frequent epileptic drug prescribed (about 20% of ASD patients) and no statistically significant differences were found across ages.

DISCUSSION

Autism is a considerable public health problem and between the initial diagnosis and the age of 18, the Italian healthcare system provides an efficient management model based on child neuropsychiatry. Child neuropsychiatry is devoted to neurological, behavioural, emotional, and psychiatric disorders in childhood and adolescence while psychiatry units usually are devoted only to psychiatric disorders, particularly in adulthood. The results from this study, based on the innovative and integrated use of healthcare and social databases, show that, in the transition to adulthood, there is a change in the models used in taking care of a child diagnosed with autism.

The use of administrative databases allowed us to study real-word diagnostic patterns of a large and unselected population. However, the diagnoses used in this analysis were made by physicians specialised in a variety of disciplines, which may lead to diagnostic imprecision. Indeed, the estimated prevalence of ASD at 8 years of age (0.54%) is lower than the autism prevalence of 1.68% reported by the most recent study [15]. Nevertheless, our estimate is very close to a value estimated in less recent years [37–39] and is similar to the prevalence reported using administrative databases in Germany during 2012 [40] for age groups ranging from 6 to 11 years (0.6%) and in France (0.35%) from register-based data [41]. In Italy, few studies reporting autism prevalence have been carried out; in a recent paper, Narzisi et al. [42] estimated a prevalence of 0.8% in 7-9 year olds. This figure is higher than ours, but the different study setting might have influenced the results, as Narzisi et al. based the study on a sample extracted at the community level. However, if we considered only children included in Narzisi et al. with both certified disability and ASD, a prevalence of 0.65% would be assessed and this

is much closer to our estimate. Since ASD is generally diagnosed after 1 year of age and our data started from 2010, we believe that only a small number of ASD-diagnosed patients who were 8 years old in 2017 were not included. Our underestimation of ASD may be due to a number of reasons: 1) a delay of diagnosis to after 8 years old; 2) a lack of recorded diagnosis in administrative databases; 3) a limited tendency to register the autism diagnosis in Lombardy by physicians; 4) a misclassification of the diagnosis; or 5) only more serious cases were diagnosed by physicians of the NHS.

With respect to incidence, we estimated for 2017 an annual incidence rate – based on administrative databases – of about 2/1000 for children aged 2-8, but we were able to find only one study for comparison [37], which estimated an annual incidence of 1.02/1000 in boys and 0.21/1000 in girls aged 2-8. This figure is lower than ours, however it referred to 2010, and the incidence of ASD in the subsequent years could have increased. Furthermore, we were able to estimate an incidence for children 2-6 years old between 2015 and 2017 and we estimated (data not shown) 4.30/1000 for 2015, 4.70 for 2016 and 7.30 for 2017. This suggests an increasing trend for ASD diagnoses reported in administrative claims that will be reflected in the prevalence of the following years. However, the increase of ASD is more related to administrative changes [13] given that fewer symptoms of autism are now required for diagnosis and that a child with a diagnosis of ASD much more often receives support at school and in the community [43], rather than a factor affecting pathogenesis.

Our study investigated the differences in rates of comorbidity and healthcare services utilisation in a selected retrospective longitudinal cohort of ASD patients from 16 to 20 years old. Given that fact, the ASD cohort used in this study included selected individuals who had been patients with health/social care services utilisation over seven years (from 2010 to 2017). Thus, the findings in this cohort could not be connected to general ASD patients during the transition age but to ASD patients who were included in a health/social services pathway and,

perhaps, having more serious conditions. Thus, our findings of a high rate (up to 66.5%) of psychiatric conditions (including mental retardation) were not completely surprising, even if higher than those reported in other studies (34% [44], 54% [5], 65% [39]). In detail, the percentage of anxiety previously reported in a previous study [44] was similar (14.4%) to ours (19.3%), as well as depression (9.9% vs 13.3%). The percentage of individuals with epilepsy in our study (9%) is comparable with other studies examining the transition age in ASD [44]. However, it must be taken into account that the diagnosis of other psychiatric conditions was also based on administrative data and thus may depend, at least in part, on which services and specialists were more involved in each patients' care.

In Italy, patients remain in charge of paediatric healthcare services until 18 years of age; however, starting at 16 years of age there may be some overlap in healthcare systems. The results of this study suggest that the type of medical services used for ASD patients changes at an age between 16 and 20 years. Further, comparison between ages showed that general healthcare services utilisation increases from 16 to 18 years old and subsequently decreases.

Neuropsychiatric and rehabilitation services decreased with age as ASD patients started to be treated by CMHS and CSS; this suggests a change in the care path for these people. Indeed, the percentage of ASD patients with at least one CMHS treatment increased from 18 to 20 years of age. Also, the percentage of ASD patients having psychiatric visits in outpatient care services or CMHS increased from 12.7% at 16 years old to 25.4% at 20 years old. This change in patients' reference services was also confirmed by the decreased rate of ASD patients with neuropsychiatric hospitalisation and the corresponding increase of psychiatric hospitalisation, even if globally the hospitalisation in dedicated departments (neuropsychiatric or psychiatric) remained stable across ages. This suggests that ASD patients and their families might look for new therapeutic references around the 18th year and then settle down, even if long-term observation may be necessary. In conclusion, we did not observe a decrease in healthcare

services utilisation as recently reported by Nathenson et al. [30]. Moreover, psychiatric healthcare services may not be the proper type of support considering the special needs (such as speech therapy, rehabilitation, and occupational therapy) of these patients.

The percentage of individuals with ASD who received at least one service related to an ED remains stable with age, although a slight increase in 17-19 year olds was observed. This suggests that even if the therapeutic references may have changed with age, this did not imply a greater need of the ED.

Even if the current evidence for the effectiveness of antipsychotic drugs in ASD is only moderate [6], neuroleptic drugs were frequently used in this cohort of ASD patients and their consumption remained stable across ages; moreover, our findings were similar to frequencies reported in other studies [39]. ADHD drugs were less prescribed (less than 0.6%) with respect to other reported prescription rates in ASD patients (about 15%) even considering the patients' age [45]; this may reflect a generally low consumption in Italy of such drugs in childhood [46].

Strengths and Limitations

The current study used large administrative databases, which made it possible to study real-world diagnostic patterns of a large and unselected population, without non-responses, interviews, or recall bias issues. However, we must note that we could not include any service utilisation outside the NHS. Furthermore, diagnoses in administrative databases are made by physicians specialised in a variety of disciplines and were not validated, which may lead to diagnostic imprecision. In addition, some diagnoses may not have been reported. With regard to the estimated rate of ASD patients who used healthcare services, we investigated what type of diagnosis these outcomes were associated with and which were the reasons for such services. However, the CSS and rehabilitation interventions database did not systematically report the type of services provided (i.e. speech therapy, rehabilitation, occupational therapy).

The 16-20 age range provides an opportunity to investigate ASD patients during the transition from paediatric to young adult services and we were able to follow longitudinally a selected group of ASD patients in transition age without the birth cohort effect. Unfortunately, our cohort was limited to adolescents with ASD who had had at least one healthcare service consumption with a diagnosis code related to ASD starting from 2010, so ASD patients who did not use healthcare services during this period would not be included. Accordingly, our findings may not be applied to all ASD patients in transition age but represented ASD patients with some healthcare service connection.

Our study suggested a change in the "therapeutic references" but we did not find a reduction in the use of healthcare services with age. However, we were not able to include a survey of caregivers in order to investigate any actual difficulties in managing this transition.

CONCLUSION

Our findings suggest that ASD patients change "therapeutic references" with age from neuropsychiatric and rehabilitative services towards psychiatric and community-based services. The rise in prevalence – based on administrative data – of ASD in children might lead to a large number of adolescents who will be entering the young adult's healthcare system in the future and will require specific support. More studies are needed to investigate the actual needs of ASD patients in order to plan future public healthcare policies and interventions.

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Contributors: ST, AGR, and MB conceived and devised the study, and ST analysed the data. All authors contributed to the interpretation of the data. ST drafted the article and AGR reviewed and edited the manuscript, and approved the version to be published, and agree to be accountable for all aspects of the work. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. ST and AGR accept full responsibility for the work and the conduct of the study, had access to the data, and controlled the decision to publish.

Compliance with Ethical Standards : The data are administrative ones, so no informed consent was necessary. The Agency of Health Protection has among its institutional functions, established by the Lombardy Region legislation, the evaluation of the care pathways of autistic patients transitioning to adulthood (DRG 7600, 20 Dec 2017, available at http://www.regione.lombardia.it/wps/wcm/connect/cf479d70-9c53-4491-b5b7-0a6d43fdcd43/DGR2017_7600_regole_2018.pdf?MOD=AJPERES&CACHEID=cf479d70-9c53-4491-b5b7-0a6d43fdcd43, page 68), which is considered a critical element to monitor at present in the Regional and National Italian Health System. Therefore, the Agency of Health Protection of Milan is allowed to use the anonymized administrative data to perform the evaluation of the services provided to autistic patients residing in the covered area. Patient identity was masked by anonymization according to the standard ISO 25237:201. Their unique identification number (fiscal code) was transcoded into a string by the Information System of the Agency of Health Protection, which had no role in analysing the data.

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Data sharing statement: The administrative data used for the present study contain sensitive information of underage people. Even though data have been anonymised we will not be able to share your data with other researchers.

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Table 1. Demographics characteristic of ASD patients at 18th years old

Calendar years of recruitment	ASD patient	Gender		Quintile of Deprivation Index					
	N. (%)	*Female % (N.)*	*Male % (N.)*	*I more rich*	*II*	*III*	*IV*	*V more poor*	*missing*
2012	69 (20.85%)	20.29% (14)	79.71% (55)	11.59% (8)	15.94% (11)	23.19% (16)	27.54% (19)	20.29% (14)	1.4% (1)
2013	75 (22.66%)	12.00% (9)	88.00% (66)	5.33% (4)	24.00% (18)	17.33% (13)	28.00% (21)	25.33% (19)	0%(0)
2014	92 (27.79%)	31.52% (29)	68.48% (63)	16.30% (15)	18.48% (17)	25.00% (23)	27.17% (25)	11.96% (11)	1%(1)
2015	95 (28.70%)	23.16% (22)	76.84% (73)	10.53% (10)	22.11% (21)	22.11% (21)	20.00% (19)	24.21% (23)	1%(1)
All	331	22.36% (74)	77.64% (257)	11.18% (37)	20.24% (67)	22.05% (73)	25.38% (84)	20.24% (67)	0.9%(3)

Table 2. Distribution of other psychiatric diagnosis and co-occurring condition by age and regression model output

	Age (years) % (N.)					Age as categorical OR (95%CI)					Age as continuous OR (95%CI)	
Conditions	**16**	**17**	**18**	**19**	**20**	**Female vs Male**	**16 vs 18**	**17 vs 18**	**19 vs 18**	**20 vs 18**	**Female vs Male**	**Age effect**
ALL CO-OCCURRING CONDITION (epilepsy included)	22.4% (74)	20.2% (67)	21.8% (72)	20.8% (69)	21.8% (72)	0.86 (0.51-1.45)	1.04 (0.83-1.29)	0.91 (0.71-1.16)	0.93 (0.77-1.12)	0.98 (0.79-1.22)	0.89 (0.53-1.50)	0.99 (0.93-1.05)
Only Epilepsy	9.1% (30)	8.2% (27)	10.3% (34)	10% (33)	9.7% (32)	0.92 (0.45-1.90)	0.87 (0.65-1.16)	0.79 (0.58-1.08)	0.97 (0.78-1.20)	0.90 (0.71-1.15)	1.01 (0.49-2.08)	1.01 (0.93-1.10)
PSYCHIATRIC DIAGNOSIS	42.6% (141)	50.8% (168)	59.8% (198)	63.7% (211)	66.5% (220)	2.06 (1.27-3.33)	0.48 (0.41-0.58)	0.68 (0.58-0.77)	1.19 (1.09-1.31)	1.36 (1.20-1.53)	2.08 (1.29-3.36)	1.30 (1.23-1.37)
F00-F09: Organic, including symptomatic, mental disorders	0.9% (3)	1.8% (6)	3.3% (11)	4.2% (14)	4.8% (16)	1.68 (0.53-5.26)	0.26 (0.10-0.70)	0.52 (0.21-1.92)	1.29 (0.97-1.71)	1.48 (1.05-2.09)	1.82 (0.60-5.54)	1.41 (1.21-1.64)
F20-F29: Schizophrenia, schizotypal and delusional disorders	11.2% (37)	16.9% (56)	20.8% (69)	23.9% (79)	26.3% (87)	1.37 (0.77-2.44)	0.47 (0.36-0.61)	0.68 (0.51-0.88)	1.20 (1.07-1.33)	1.37 (1.19-1.57)	1.33 (0.75-2.35)	1.27 (1.20-1.36)
F30-F39: Mood [affective] disorders	2.7% (9)	6.3% (21)	8.5% (8)	10.6% (35)	13.3% (44)	3.25 (1.62-6.50)	0.29 (0.17-0.51)	0.74 (0.57-1.91)	1.29 (1.07-1.55)	1.69 (1.32-2.16)	3.14 (1.61-6.14)	1.43 (1.30-1.59)
F40-F48: Neurotic, stress-related and somatoform disorders	6.9% (23)	10.6% (35)	13.6% (45)	16.9% (56)	19.3% (64)	1.46 (0.77-2.78)	0.48 (0.35-0.65)	0.71 (0.62-2.89)	1.31 (1.12-1.53)	1.55 (1.28-1.88)	1.44 (0.76-2.72)	1.31 (1.21-1.42)
F60-F69: Disorders of adult personality and behaviour	5.7% (19)	9.1% (30)	13.3% (44)	16.9% (56)	18.7% (62)	2.28 (1.23-4.25)	0.39 (0.26-0.57)	0.67 (0.51-0.80)	1.34 (1.14-1.58)	1.53 (1.26-1.84)	2.14 (1.16-3.94)	1.35 (1.25-1.47)
F70-F79: Mental retardation	26.9% (89)	29.9% (99)	35% (116)	37.2% (123)	39% (129)	1.52 (0.92-2.52)	0.68 (0.59-0.78)	0.72 (0.71-0.88)	1.10 (1.02-1.18)	1.19 (1.08-1.30)	1.52 (0.92-2.51)	1.15 (1.10-1.20)
F90-F98: Behavioural and emotional disorders with onset usually occurring in childhood and adolescence	10.6% (35)	11.2% (37)	12.7% (42)	14.2% (47)	15.4% (51)	1.01 (0.48-2.11)	0.81 (0.70-0.95)	0.86 (0.76-0.98)	1.11 (1.00-1.23)	1.23 (1.07-1.41)	1.01 (0.49-2.12)	1.11 (1.05-1.17)

Table 3. Analysis of the access to health / social services in ASD patients and Odds ratio (OR) and corresponding confidence intervals from logistic regression

	Age (years) % (N.)					Female vs Male	Age as categorical OR (95%CI)				Age as continuous OR (95%CI)	
	16	17	18	19	20		16 vs 18	17 vs 18	19 vs 18	20 vs 18	Female vs Male	Age effect
Global access	46.5% (154)	58.6% (194)	68% (225)	57.4% (190)	54.1% (179)	1.40 (0.95-2.07)	0.47 (0.35-0.64)	0.73 (0.56-0.96)	0.55 (0.42-0.72)	0.44 (0.33-0.59)	1.36 (0.92-2)	0.97 (0.9-1.06)
Visit neuropsychiatry as outpatient	15.4% (51)	25.1% (83)	30.8% (102)	10% (33)	5.4% (18)	1.19 (0.77-1.85)	0.47 0.34-0.67)	0.79 (0.59-1.07)	0.25 (0.17-0.36)	0.12 (0.07-0.20)	1.15 (0.76-1.74)	0.76 (0.69-0.84)
Visit Neurology as outpatient	4.5% (15)	3.3% (11)	4.8% (16)	6.6% (22)	10.6% (35)	1.66 (0.87-3.19)	1.11 (0.55-2.22)	0.78 (0.38-1.60)	1.47 (0.83-2.61)	2.52 (1.45-4.38)	1.68 (0.87-3.22)	1.29 (1.10-1.53)
Visit Psychiatry as outpatient	12.7% (42)	10% (33)	13.6% (45)	13.6% (45)	14.8% (49)	0.95 (0.64-1.41)	0.97 (0.62-1.50)	0.75 (0.48-1.19)	1.01 (0.65-1.57)	1.07 (0.70-1.64)	0.94 (0.64-1.40)	1.05 (0.94-1.17)
Test as outpatient	6.6% (22)	6.6% (22)	8.5% (28)	3% (10)	1.8% (6)	1.05 (0.59-1.87)	0.78 (0.42-1.46)	0.78 (0.45-1.33)	0.33 (0.16-0.71)	0.2 (0.08-0.46)	1.06 (0.60-1.87)	0.76 (0.65-0.87)
Rehabilitation as outpatient	19.9% (66)	20.2% (67)	16.9% (56)	3.9% (13)	3.9% (13)	1.09 (0.65-1.83)	1.38 (0.97-1.96)	1.33 (0.99-1.79)	0.2 (0.11-0.35)	0.19 (0.11-0.34)	1.09 (0.65-1.81)	0.62 (0.56-0.69)
Psychological support as outpatient	15.1% (50)	13.3% (44)	12.1% (40)	6.3% (21)	3.3% (11)	1.74 (1.02-2.98)	1.37 (0.95-1.98)	1.18 (0.81-1.73)	0.47 (0.3-0.73)	0.25 (0.13-0.48)	1.74 (1.02-2.98)	1.37 (0.95-1.98)
ED access[a]	19.3% (64)	22.7% (75)	23.3% (77)	21.5% (71)	19% (63)	1.22 (0.82-1.81)	0.91 (0.64-1.28)	1.03 (0.73-1.44)	0.86 (0.62-1.20)	0.72 (0.51-1.01)	1.22 (0.82-1.81)	0.94 (0.86-1.02)
CMHS	0% (0)	0.9% (3)	15.1% (50)	19.3% (64)	20.8% (69)	0.9 (0.5-1.63)	-	-	1.27 (0.97-1.66)	1.33 (0.99-1.78)	0.88 (0.49-1.6)	1.15 (0.99-1.32)
Rehabilitation	17.8% (59)	13.3% (44)	11.5% (38)	4.8% (16)	1.8% (6)	1.33 (0.73-2.43)	1.77 (1.35-2.33)	1.22 (1.02-1.45)	0.38 (0.25-0.59)	0.14 (0.06-0.30)	1.43 (0.79-2.59)	0.61 (0.54-0.68)
Psychiatry visits outpatient and CMHS	12.7% (42)	10.3% (34)	17.8% (59)	23.6% (78)	25.4% (84)	1 (0.66-1.52)	0.78 (0.52-1.16)	0.57 (0.37-0.86)	1.39 (1.02-1.9)	1.48 (1.08-2.02)	0.99 (0.65-1.5)	1.22 (1.11-1.35)
Hospital admission	16.9% (56)	22.4% (74)	16.9% (56)	19.3% (64)	16% (53)	1.12 (0.75-1.66)	1.42 (0.98-2.05)	1.80 (1.25-2.59)	1.11 (0.78-1.59)	0.82 (0.54-1.23)	1.12 (0.75-1.66)	0.86 (0.78-0.94)
Psychiatry ward	1.2% (4)	2.7% (9)	5.7% (19)	8.5% (28)	6.3% (21)	1.24 (0.68-2.28)	0.29 (0.1-0.79)	0.54 (0.26-1.12)	1.44 (0.89-2.33)	0.97 (0.54-1.74)	1.26 (0.69-2.29)	1.28 (1.1-1.49)
Neuropsychiatry ward	8.8% (29)	10.3% (34)	4.5% (15)	0.9% (3)	0.3% (1)	1.89 (0.97-3.7)	3.18 (1.77-5.72)	3.19 (1.84-5.52)	0.18 (0.05-0.59)	0.06 (0.01-0.38)	1.96 (1-3.84)	0.44 (0.38-0.51)
Psychiatry and neuropsychiatry ward	9.4% (31)	10.6% (35)	9.4% (31)	9.4% (31)	6.6% (22)	1.40 (0.85-2.31)	1.48 (0.92-2.40)	1.43 (0.92-2.22)	0.93 (0.59-1.47)	0.59 (0.35-1.01)	1.41 (0.86-2.32)	0.80 (0.7-0.91)
Residential facility	6.6% (22)	6.3% (21)	8.8% (29)	7.3% (24)	6% (20)	0.97 (0.45-2.05)	0.82 (0.52-1.30)	0.76 (0.53-1.10)	0.77 (0.54-1.09)	0.66 (0.43-1.01)	1.00 (0.47-2.13)	0.95 (0.81-1.10)
CSS	4.8% (9)[a]	11.1% (29)[a]	18.4% (61)	20.5% (68)	21.8% (72)	1.46 (0.78-2.74)	0.20 (0.1-0.41)	0.51 (0.37-0.7)	1.15 (1-1.32)	1.21 (1.02-1.45)	1.49 (0.81-2.73)	1.33 (1.22-1.45)

[a] Since databases started from 2012 as denominator we included only contributing age after 2012

(Cont'd)

Table 3. (Continue) Analysis of the access to health / social services in ASD patients and Odds ratio (OR) and corresponding confidence intervals from logistic regression

	Age (years) % (N.)						Age as categorical OR (95%CI)				Age as continuous OR (95%CI)	
	16	17	18	19	20	Female vs Male	16 vs 18	17 vs 18	19 vs 18	20 vs 18	Female vs Male	Age effect
All neuroleptic prescriptions [b]	35.6% (118)	39.3% (130)	44.7% (148)	45% (149)	44.1% (146)	1.18 (0.74-1.88)	0.91 (0.74-1.14)	0.93 (0.78-1.10)	0.94 (0.78-1.13)	0.85 (0.68-1.07)	1.18 (0.74-1.89)	0.98 (0.92-1.05)
Antidepressant (N06A)	5.7% (19)	7.9% (26)	10.6% (35)	9.4% (31)	11.2% (37)	2.54 (1.40-4.64)	0.63 (0.40-0.98)	0.78 (0.54-1.15)	0.81 (0.58-1.15)	0.99 (0.66-1.50)	2.50 (1.37-4.55)	1.10 (0.98-1.24)
Antipsychotic (N05)	27.8% (92)	30.8% (102)	33.8% (112)	34.1% (113)	34.7% (115)	0.57 (0.34-0.96)	1.04 (0.72-1.49)	1.01 (0.75-1.36)	0.92 (0.69-1.22)	0.91 (0.65-1.27)	0.57 (0.34-0.96)	0.97 (0.87-1.07)
Anxiolytic (N05B, N05CD, N05CF)	0.9% (3)	1.8% (6)	1.5% (5)	1.5% (5)	1.5% (5)	3.63 (0.84-15.61)	0.70 (0.24-2.04)	1.48 (0.76-2.85)	0.91 (0.34-2.42)	1.06 (0.43-2.66)	6.00 (1.37-26.24)	1.06 (0.80-1.41)
Antiepileptic (NO3A)	16.3% (54)	16.3% (54)	20.8% (69)	23.0% (76)	23.9% (79)	1.22 (0.71-2.08)	0.91 (0.72-1.16)	0.84 (0.68-1.03)	1.11 (0.92-1.34)	1.13 (0.90-1.41)	1.22 (0.72-2.08)	1.06 (0.99-1.13)
AHDH prescriptions (NO6BA)	0.6% (2)	0.6% (2)	0.6% (2)	0% (0)	0.3% (1)							
Risperidone and/or Aripiprazole (N05AX08, N05AX12)	20.2% (67)	21.8% (72)	23.6% (78)	25.4% (84)	24.2% (80)	0.82 (0.49-1.36)	1.14 (0.86-1.52)	1.09 (0.87-1.36)	1.08 (0.89-1.31)	0.97 (0.76-1.23)	0.81 (0.48-1.34)	0.96 (0.89-1.04)
Risperidone (N05AX08)	15.7% (52)	15.4% (51)	15.7% (52)	15.4% (51)	15.4% (51)	0.54 (0.31-0.94)	1.32 (0.97-1.80)	1.15 (0.89-1.48)	0.93 (0.72-1.20)	0.90 (0.67-1.20)	0.54 (0.31-0.94)	0.91 (0.83-0.99)
Aripiprazole (N05AX12)	5.1% (17)	8.5% (28)	10.3% (34)	11.5% (38)	10.9% (36)	1.47 (0.74-2.92)	0.66 (0.40-1.08)	0.99 (0.70-1.40)	1.14 (0.86-1.50)	1.04 (0.73-1.50)	1.47 (0.73-2.94)	1.09 (0.97-1.24)
Valproic acid (N03AG01)	12.7% (42)	10.9% (36)	15.4% (51)	16.3% (54)	18.1% (60)	1.02 (0.54-1.92)	1.01 (0.77-1.33)	0.77 (0.58-1.02)	1.04 (0.84-1.30)	1.15 (0.88-1.49)	1.02 (0.55-1.88)	1.04 (0.96-1.13)

[b] ATC code "N" (nervous system) excluding anaesthetics (N01) and analgesics (N02)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3/4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	-
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*6-8*
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	-
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7-8
		(*b*) Describe any methods used to examine subgroups and interactions	7-8
		(*c*) Explain how missing data were addressed	-
		(*d*) If applicable, explain how loss to follow-up was addressed	-
		(*e*) Describe any sensitivity analyses	-
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	-
		(c) Consider use of a flow diagram	-
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8;22
		(b) Indicate number of participants with missing data for each variable of interest	22
		(c) Summarise follow-up time (eg, average and total amount)	-
Outcome data	15*	Report numbers of outcome events or summary measures over time	8-10; 23-25
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	-
		(*b*) Report category boundaries when continuous variables were categorized	-
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	-
Discussion			
Key results	18	Summarise key results with reference to study objectives	15
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14-15
Generalisability	21	Discuss the generalisability (external validity) of the study results	14-15
Other information			12
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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DO AUTISTIC PATIENTS CHANGE HEALTHCARE SERVICES UTILISATION THROUGH THE TRANSITION-AGE? AN ITALIAN LONGITUDINAL RETROSPECTIVE STUDY

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DO AUTISTIC PATIENTS CHANGE HEALTHCARE SERVICES UTILISATION THROUGH THE TRANSITION-AGE? AN ITALIAN LONGITUDINAL RETROSPECTIVE STUDY

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Keywords: Autism spectrum disorder; Epidemiology; Administrative databases; Health outcomes; Health service research

DO AUTISTIC PATIENTS CHANGE HEALTHCARE SERVICES UTILISATION THROUGH THE TRANSITION-AGE? AN ITALIAN LONGITUDINAL RETROSPECTIVE STUDY

ABSTRACT

Objectives: The purpose of this paper is to provide an estimate of the prevalence rate of autism spectrum disorder (ASD) at 8 years of age in 2017 based on administrative databases and to investigate the change in healthcare services use during the transition-age.

Design: Longitudinal retrospective cohort study

Setting: Administrative Healthcare Database (2010-2017) in Italy

Participants: We identified 5,607 ASD patients; 331 ASD patients from 2012 to 2015 in the calendar year of their 18th birthday were selected and their health service utilisation during a 5-year period - the two years preceding and succeeding their 18th year - were investigated.

Interventions: none

Primary and secondary outcome measures: Prevalence, incidence, and proportion of ASD patients receiving specific healthcare services

Results: Prevalence of ASD at age 8 was 5.4/1,000. Global access to health and social services was lower both before and after age 18 (46.5% at 16, 68% at 18, 54.1% at 20). The percentage of patients receiving a neuropsychiatric consultation decreased after age 18 (30.8% at 18, 5.4% at 20). Community mental health services (CMHS) utilisation rate increased above 18 years of age. Regarding psychiatric visits, for both outpatient and CMHS services, an increase was observed from 17.8% at age 18 to 25.4% at age 20. The utilisation of rehabilitation services decreased with age, going from 17.8% at age 16 to 1.8% at age 20. Psychiatric outpatient services remained stable across ages at about 14%.

Conclusions: Our findings suggest that ASD patients changed "therapeutic references" with age from neuropsychiatric and rehabilitative services towards psychiatric and community-based services as they transitioned from paediatric to young adult's healthcare services.

Keywords: Autism spectrum disorder; Epidemiology; Administrative databases; Health outcomes; Health service research

Strengths and limitations of this study

- Longitudinal retrospective cohort study based on Administrative Healthcare Database: real-world diagnostic patterns of a large and unselected population (3.5 million habitants)
- Estimation of prevalence and incidence rates, differences in comorbidity, and healthcare services utilisation in an unselected retrospective longitudinal cohort of ASD patients from 16 to 20 years of age
- Diagnosis codes and healthcare services utilisation were based only on the administrative data

INTRODUCTION

Autism spectrum disorder (ASD) is a brain-based chronic neurodevelopmental disorder with lifelong impacts. It is characterised and diagnosed by impairments in social communication and social interaction with the presence of restricted, repetitive behaviours [1]. Onset of ASD typically occurs by age 3, although some studies suggest that symptoms can emerge between 6 and 18 months of age and may not be fully manifested until school age [2,3]. Children, adolescents, and adults with ASD can often present a number of comorbidities including psychiatric conditions, intellectual disabilities, developmental delay, epilepsy, anxiety, language and motor difficulties, and depression [4–7].

The aetiology of ASD remains largely unexplained. It seems to be highly heritable [8] and some environmental risk factors [9] and parental age [10] may be involved. The prevalence of ASD has increased in the last decades, although the reasons for this increase are not fully understood. It might be related to etiologic, non-etiologic, and administrative factors (e.g. modified diagnostic criteria, improved access to services, and increased public and scientific interest [6,11,12]).

A review published in 2012 [13] estimated the global prevalence of ASD to be about 1% (62/10000); a more recent study has estimated the prevalence to be 1.5% in developed countries [14–16]. In 2014 [15], a prevalence rate of 16.8 per 1000 was estimated for children aged 8.

Treatments for ASD vary across the world and even within country regions and it has been reported that parents with a lower educational level are less successful in obtaining specialist interventions that could improve outcomes [6]. Treatments for ASD include early parent-mediated interventions and behavioural and social treatments. Evidence-based pharmacology in ASD is currently limited to the treatment of co-occurring behaviours or diagnoses and not ASD itself [6]. Risperidone [17] and aripiprazole [18] have improved

symptoms of irritability or agitation in children and adolescents with ASD. Methylphenidate [19], atomoxetine [20], and guanfacine [21] have shown a benefit for ADHD symptoms in ASD. However, the use of such drugs presents some adverse effects and their use has been indicated during a specific age period.

While autism is generally considered a disorder of childhood, the rise in ASD prevalence in the last decades has produced an increase of individuals with ASD transitioning from paediatric to young adult medical services resulting in autism rapidly becoming a disorder of adulthood as well [22]. There is evidence that for young people with special healthcare needs, such as autism, transitioning form paediatric to adult healthcare represents a problem [23,24]. The transition process may be especially difficult for young people whose special healthcare needs involve mental health, developmental disabilities, or intellectual disabilities [24]. Moreover, the lack of ASD treatment guidelines for adult patients increases the complexity of healthcare delivery and involves a problematic transition from paediatric to adult healthcare [25]. Very often, the transition to adulthood in people with ASD results in poor outcomes across multiple domains including employment, education, healthcare, social engagement, and independent living [26,27], even in the presence of healthcare transition services [28]. This may represent problems both for parents [27] and patients [29].

Often the transition from the paediatric to adult healthcare system coincides with an exit from the educational system (i.e. high school) where adolescents may receive daily support that may further affect service usage. However, to our knowledge, only a few studies have described changes in healthcare service usage during the transition to adulthood in people with ASD [24,26,30]. Administrative claims data can be plentiful, comprehensive, cost efficient, and free from some of the biases that accompany other types of data, such as surveys or self-reports [31]. Analyses of administrative healthcare databases have the potential to include a large number of individuals and have been successfully used in the study of health outcomes associated with a

variety of conditions [31,32]. Studies conducted in the US [33] and Canada [34,35] have indicated that administrative claims data were able to clearly identify children with ASD.

The purpose of this paper is to provide an estimate of the prevalence of ASD at 8 years of age using administrative databases derived from the largest Northern Italian population. Further, this study investigated the change in healthcare services use during the transition from the paediatric to young adult healthcare systems.

METHODS

Data collection

A retrospective cohort study was conducted using the Administrative Healthcare Database of the Agency for Health Protection of Milan (AHD-ATS) from January 1, 2010 to December 31, 2017. Only data regarding patients residing in the ATS were considered. In Italy, the National Healthcare System (NHS) is universal and fully covers the population and the ATS provides care to about 3,500,000 inhabitants.

Data were obtained from AHD-ATS, which included 8 different databases: 1) outpatient activity data (6 million (M) records), such as visits and tests performed by residents in the study area in ambulatories and laboratories; 2) hospital discharge records (1M); 3) co-payment Exemption Register (1M); 4) emergency department (ED) visits (2M); 5) rehabilitation interventions database (800,000), such as visits and rehabilitative therapy (i.e. speech therapy, physiotherapy, and educative and occupational therapy); 6) community mental health services (CMHS) (100,000) such as psychiatry visits, residential facilities, pharmacological interventions, and family support in psychiatric setting; 7) pharmaceutical prescription database (200M); and 8) community and social services (CSS) (1M) such as family support, day care centres, community and residential facilities, home care, home care economic aid, and hospice.

These databases can be linked through a unique identifier code; demographic information was obtained by record linkage using a unique identifier code with patients' master

data and Deprivation Index by using record linkage with the 2001 General Census of Population and Housing.

ASD patients were defined as individuals having a reported diagnosis of ASD (ICD-9 codes 299.00 to 299.99 or their ICD-10 equivalents) in at least one of the databases during the study period [35]. For each patient, the calendar year of birth was used as an approximate age value at the time of service utilisation.

Statistical analysis

Prevalence and incidence rates estimation

Prevalence rates at age 8 and 2-8 years incidence rates based on administrative databases were estimated for 2017. The prevalence rate was obtained by dividing the number of children 8 years old diagnosed as ASD in 2017 or previously, by the population size – of the same age – in the study area at 1 January 2018 based on the Italian National Institute of Statistics.

The annual incidence rates were obtained by dividing the annual number of children aged 2-8 years newly diagnosed by the general population subtracting the number of ASD diagnoses in preceding years. Binomial 95% confidence intervals (95%CI) were calculated for the prevalence and incidence rates.

Consumptions and outcome models

We selected ASD patients from 2012 to 2015 in the calendar year of their 18th birthday, and we investigated Health Services utilisation during a 5-year period: the two years preceding and succeeding their 18th year as well as the year of their 18th birthday (i.e. aged from 16 to 20). We investigated the percentage of co-occurring conditions related to other psychiatric diseases; as an outcome variable, we investigated access to services (i.e. outpatient, rehabilitation interventions, community/social services, ED access, hospital admissions, and neuroleptic drug consumption).

Co-occurring conditions were identified by using the chronicity database [36] that covers the 13 main comorbidity conditions (hypertension, diabetes, dyslipidaemia, COPD, heart failure, renal failure, neoplasms, cardiovascular diseases, inflammatory bowel disease, chronic liver diseases, chronic neurological diseases, autoimmune diseases, and endocrine and metabolic diseases). The proportion of ASD patients with a co-occurring psychiatric diagnosis was estimated searching for psychiatric diagnoses (ICD-10 code: F00 to F99, F84 (autistic disorder) excluded, and their ICD-9 conversion according to the database encoding) in the AHD-ATS databases; we assumed that the psychiatric conditions persisted over time after the first psychiatric diagnoses were recorded.

As outcomes, we investigated consumption of outpatient services (psychiatric, neurologic, and neuropsychiatric visits; tests and psychological services), ED admissions, rehabilitation interventions, CMHS interventions, hospital admissions (psychiatry and neuropsychiatric hospitalisation), residential services, and CSS utilisations.

With regard to neuroleptic drug consumption, we investigated the percentages of ASD patients who had at least one prescription for any psychotropic substances according to the anatomical therapeutic chemical (ATC) classification. We selected all substances with ATC code "N" (nervous system) excluding anaesthetics (N01) and analgesics (N02). In addition, we included antidepressants (N06A), antipsychotics (N05), anxiolytics/tranquillisers (N05B, N05CD, N05CF), ADHD medication (N06BA), and antiepileptics (N03A) as separate groups. risperidone (N05AX08), aripiprazole (N05AX12), and valproic acid (N03AX09) consumption was also considered.

The binary responses of co-occurring diseases, other psychiatric diagnoses, service consumptions, and outcomes at ages 16-20 were modelled by repeated measurements using a generalised estimating equation (GEE) approach with a dichotomic response variable. The binary responses for individual ASD patients were assumed to be equally correlated, so an

exchangeable correlation structure was assumed; ages were modelled first as a categorical variable with age 18 as reference. Regressions for co-occurring diseases and other psychiatric diagnoses were adjusted by a gender and deprivation index; in addition, logistic regressions for service consumption and outcomes were adjusted for co-occurring diseases and other psychiatric diagnoses.

Patient and public involvement

Neither patients nor the public were involved in the design or conduct of this study.

RESULTS

In the period between 2010 and 2017, we identified 5,607 patients (4,109 male and 1,498 female) who met the inclusion criteria. Mean age as at 2017 was 22 years (min-max 1-90), 19 years old for males (min-max 1-88) and 30 years for females (min-max 2-90). Based on administrative data, the prevalence of ASD at 8 years old on 31 December 2017 was 5.4/1,000 inhabitants (95%CI 4.6-6.2); prevalence for males was about three times that of females: 8.1/1,000 (95%CI 6.8-9.5) for males and 2.6/1,000 inhabitants (95 % CI 1.8-3.5) for females. The incidence rate for 2-8 years in 2017 was 2.1 per 1,000 inhabitants/year (95%CI 1.9-2.3). Incidence in males was higher than in females: 3.3 (95%CI 1.9-2.3) for males and 0.8 per 1,000 inhabitants/year (95%CI 0.6-0.9) for females.

We included all patients (331) who were 18 years old between 2012 and 2015 (Table 1), of whom 257 (77.64%) were male and 74 (22.36%) were female. With regard to the deprivation index, at 18 years of age, 11.18% were in the least deprived quintile while 20.24% were in the most deprived quintile; no differences were found in the quintile distribution by calendar year (*p*-value=0.2).

Co-occurring conditions (Table 2) were present in about 22% of patients at 16 years of age and remained constant among ages; no differences were found for gender or deprivation index. In contrast, other psychiatric diagnoses increased from 42.6% at 16 years of age to 66.5%

at age 18 (p-value <0.001); females had a greater risk than males (p-value=0.003) and no differences were found for the deprivation index.

The most reported psychiatric condition was mental retardation (F70-F79) at over 30%; schizophrenia, schizotypal, and delusional disorders (F20-F29) were over 20%; anxiety, dissociative, stress-related, somatoform, and other nonpsychotic mental disorders (F40-F48) were about 20%. Behavioural and emotional disorders F90-F98 reached 15.4%.

Schizotypal and delusional disorders increased from 11.2% at 16 years old to 26.3% at age 18 (p-value=0.001); at 16 years old about 30% of individuals with ASD had intellectual disabilities, and that percentage increased with age reaching 39% at 20 years (p-value <0.001). We found a greater risk for females regarding mood affecting disorders (F30-F39, p-value <0.001) and disorders of adult personality and behaviour (F60-F69, p-value=0.009).

The percentage of ASD patients with at least one access to health services by age is reported in Table 3. Global access to health and social services are lower both before and after age 18 (Table 3), with comparable levels at 16 and 20 years of age (p-value=0.08).

The percentage of patients receiving a neuropsychiatric consultation (Table 3) decreases after 18 years of age (from 30.8% at age 18 to 5.4% at age 20, OR=0.12; 95%CI 0.07-0.32). However, neurologist visits increase after 18 years of age (4.9% at age 18 to 10.6% at 20, OR=2.52; 95%CI 1.45-4.38) and only at 20 years of age reach statistical significance compared to age 18. Psychiatric outpatient visits remained stable across all ages (14%). Healthcare provided as outpatient services showed a statistically significant decrease after 18 years of age (i.e. psychological services (from 15.1% at age 18 to 3.3% at age 20, OR_{20vs18}=0.25; 95%CI 0.13-0.48); rehabilitative services (from 19.9% to 3.9%, OR_{20vs18}=0.19; 95%CI 0.11-0.34); and tests (from 6.6% to 1.8%, OR_{20vs18}=0.20; 95%CI 0.08-0.46)). The ED admission figure showed a significant increase from 16 years of age (19.3%) to age 18 (23.3%, OR_{16vs18} 0.91 95%CI 0.64-1.28) and then decreased to 19% (OR_{20vs18}=0.72; 95%CI 0.52-1.01) at age 20.

As CMHS usually take care of adult patients, access to this service was investigated starting from 18 years of age. No access to CMHS was recorded before age 18 and an increase in the utilisation rate was found over age 18 (from 15.1% at age 18 to 20.8% at age 20, OR_{20vs18}=1.33; 95%CI 0.99-1.78). With regard to psychiatric visits both in outpatient services and CMHS, a rate increase was observed after 18 years of age, from 17.8% at age 18 to 25.4% at age 20 (OR_{20vs18}=1.48; 95%CI 1.08-2.02). The utilisation of rehabilitation services decreased with age, going from 17.8% at age 18 to 1.8% at age 20 (OR_{20vs18}=0.38; 95%CI 0.25-0.59).

Global hospital admissions decreased with age, with a significant decrease at 18 years of age compared to age 17 (from 22.4% at age 17 to 16.9% at age 18, OR_{17vs18}=1.80; 95%CI 1.25-2.59). Neuropsychiatric and psychiatric hospital admissions showed opposite trends: neuropsychiatric accesses decreased with age (from 8.8% at age 18 to 0.3% at age 20, OR_{20vs18}=0.06; 95%CI 0.01-0.38) while psychiatric accesses increased (from 1.2% at age 18 to 6.3% at age 20, OR_{20vs18}=0.97; 95%CI 0.54-1.74). It should be noted that neuropsychiatric and psychiatric hospital admissions together remained stable across ages (9.4% at age 16 to 6.6% at age 20, OR_{20vs18}=0.59; 95%CI 0.35-1.01).

More than 40% of ASD patients had neurological drug prescriptions, and the percentage increased with age, although the increase was not statistically significant. Antipsychotics (about 30%) and antiepileptics (about 20%) were the most commonly prescribed drugs and these percentages did not show a statistically significant increase with age. In detail, risperidone (15%) and aripiprazole (from 5% to 11.5%) were the antipsychotic drugs most frequently prescribed. Valproic acid was the most frequent epileptic drug prescribed (about 20% of ASD patients) and no statistically significant differences were found across ages.

DISCUSSION

Autism is a considerable public health problem and between the initial diagnosis and the age of 18, the Italian healthcare system provides an efficient management model based on child neuropsychiatry. Child neuropsychiatry is devoted to neurological, behavioural, emotional, and psychiatric disorders in childhood and adolescence while psychiatry units usually are devoted only to psychiatric disorders, particularly in adulthood. The results from this study, based on the innovative and integrated use of healthcare and social databases, show that, in the transition to adulthood, there is a change in the models used in taking care of a child diagnosed with autism.

The use of administrative databases allowed us to study real-word diagnostic patterns of a large and unselected population. However, the diagnoses used in this analysis were made by physicians specialised in a variety of disciplines, which may lead to diagnostic imprecision. Indeed, the estimated prevalence of ASD at 8 years of age (0.54%) is lower than the autism prevalence of 1.68% reported by the most recent study [15]. Nevertheless, our estimate is very close to a value estimated in less recent years [37–39] and is similar to the prevalence reported using administrative databases in Germany during 2012 [40] for age groups ranging from 6 to 11 years (0.6%) and in France (0.35%) from register-based data [41]. In Italy, few studies reporting autism prevalence have been carried out; in a recent paper, Narzisi et al. [42] estimated a prevalence of 0.8% in 7-9 year olds. This figure is higher than ours, but the different study setting might have influenced the results, as Narzisi et al. based the study on a sample extracted at the community level. However, if we considered only children included in Narzisi et al. with both certified disability and ASD, a prevalence of 0.65% would be assessed and this is much closer to our estimate. Since ASD is generally diagnosed after 1 year of age and our data started from 2010, we believe that only a small number of ASD-diagnosed patients who were 8 years old in 2017 were not included. Our underestimation of ASD may be due to a number of reasons: 1) a delay of diagnosis to after 8 years old; 2) a lack of recorded diagnosis

in administrative databases; 3) a limited tendency to register the autism diagnosis in Lombardy by physicians; 4) a misclassification of the diagnosis; or 5) only more serious cases were diagnosed by physicians of the NHS.

With respect to incidence, we estimated for 2017 an annual incidence rate – based on administrative databases – of about 2/1000 for children aged 2-8, but we were able to find only one study for comparison [37], which estimated an annual incidence of 1.02/1000 in boys and 0.21/1000 in girls aged 2-8. This figure is lower than ours, however it referred to 2010, and the incidence of ASD in the subsequent years could have increased. Furthermore, we were able to estimate an incidence for children 2-6 years old between 2015 and 2017 and we estimated (data not shown) 4.30/1000 for 2015, 4.70 for 2016 and 7.30 for 2017. This suggests an increasing trend for ASD diagnoses reported in administrative claims that will be reflected in the prevalence of the following years. However, the increase of ASD is more related to administrative changes [12] given that fewer symptoms of autism are now required for diagnosis and that a child with a diagnosis of ASD much more often receives support at school and in the community [43], rather than a factor affecting pathogenesis.

Our study investigated the differences in rates of comorbidity and healthcare services utilisation in a retrospective longitudinal cohort of ASD patients from 16 to 20 years old. Given that fact, the ASD cohort used in this study included individuals who had been patients with health/social care services utilisation over seven years (from 2010 to 2017). Thus, the findings in this cohort could not be connected to general ASD patients during the transition age but to ASD patients who were included in a health/social services pathway and, perhaps, having more serious conditions. Thus, our findings of a high rate (up to 66.5%) of psychiatric conditions (including mental retardation) were not completely surprising, even if higher than those reported in other studies (34% [44], 54% [5], 65% [39]). In detail, the percentage of anxiety previously reported in a previous study [44] was similar (14.4%) to ours (19.3%), as well as

depression (9.9% vs 13.3%). The percentage of individuals with epilepsy in our study (9%) is comparable with other studies examining the transition age in ASD [44]. We observed a high percentage of schizophrenia, schizotypal and delusional disorders (over 20%) compared to other studies (between 8% in adults [5,45,46] and 17% in 22-40 years old [7]). This could be related to a change from child neuropsychiatry services to psychiatry services in the young adult phase where personality disorders are probably over-diagnosed. Moreover it must be taken into account that the diagnosis of other psychiatric conditions was also based on administrative data and thus may depend, at least in part, on which services and specialists were more involved in each patients' care. Surprisingly, we observed an increasing rate of intellectual disability from 16 years to 20; this could be related to two possible causes. On one hand, this trend may be related to the end of the pediatric co-payment exemption at age 18 that before could overwrite other causes of exemption. On the other hand, the end of compulsory education may cause an increase of intellectual assessment request in order to provide a more specific daily support. In Italy, patients remain in charge of paediatric healthcare services until 18 years of age; however, starting at 16 years of age there may be some overlap in healthcare systems. The results of this study suggest that the type of medical services used for ASD patients changes at an age between 16 and 20 years. Further, comparison between ages showed that general healthcare services utilisation increases from 16 to 18 years old and subsequently decreases.

Neuropsychiatric and rehabilitation services decreased with age as ASD patients started to be treated by CMHS and CSS; this suggests a change in the care path for these people. Indeed, the percentage of ASD patients with at least one CMHS treatment increased from 18 to 20 years of age. Also, the percentage of ASD patients having psychiatric visits in outpatient care services or CMHS increased from 12.7% at 16 years old to 25.4% at 20 years old. This change in patients' reference services was also confirmed by the decreased rate of ASD patients with neuropsychiatric hospitalisation and the corresponding increase of psychiatric hospitalisation,

even if globally the hospitalisation in dedicated departments (neuropsychiatric or psychiatric) remained stable across ages. This suggests, together whit the higher global access observed at 18th , that ASD patients and their families might look for new therapeutic references around the 18th year and then settle down, even if long-term observation may be necessary. In conclusion, we did not observe a decrease in healthcare services utilisation as recently reported by Nathenson et al. [30]. Moreover, psychiatric healthcare services may not be the proper type of support considering the special needs (such as speech therapy, rehabilitation, and occupational therapy) of these patients.

The percentage of individuals with ASD who received at least one service related to an ED remains stable with age, although a slight increase in 17-19 year olds was observed. This suggests that even if the therapeutic references may have changed with age, this did not imply a greater need of the ED.

Even if the current evidence for the effectiveness of antipsychotic drugs in ASD is only moderate [6], neuroleptic drugs were frequently used in this cohort of ASD patients and their consumption remained stable across ages; moreover, our findings were similar to frequencies reported in other studies [39]. ADHD drugs were less prescribed (less than 0.6%) with respect to other reported prescription rates in ASD patients (about 15%) even considering the patients' age [47]; this may reflect a generally low consumption in Italy of such drugs in childhood [48].

Strengths and Limitations

The current study used large administrative databases, which made it possible to study real-world diagnostic patterns of a large and unselected population, without non-responses, interviews, or recall bias issues. However, we must note that we could not include any service utilisation outside the NHS. Furthermore, diagnoses in administrative databases are made by physicians specialised in a variety of disciplines and were not validated, which may lead to diagnostic imprecision. In addition, some diagnoses may not have been reported. With regard

to the estimated rate of ASD patients who used healthcare services, we investigated what type of diagnosis these outcomes were associated with and which were the reasons for such services. However, the CSS and rehabilitation interventions database did not systematically report the type of services provided (i.e. speech therapy, rehabilitation, occupational therapy).

The 16-20 age range provides an opportunity to investigate ASD patients during the transition from paediatric to young adult services and we were able to follow longitudinally a group of ASD patients in transition age without the birth cohort effect. Unfortunately, our cohort was limited to adolescents with ASD who had had at least one healthcare service consumption with a diagnosis code related to ASD starting from 2010, so ASD patients who did not use healthcare services during this period would not be included. Accordingly, our findings may not be applied to all ASD patients in transition age but represented ASD patients with some healthcare service connection.

Our study suggested a change in the "therapeutic references" but we did not find a reduction in the use of healthcare services with age. However, we were not able to include a survey of caregivers in order to investigate any actual difficulties in managing this transition.

CONCLUSION

Our findings suggest that ASD patients change "therapeutic references" with age from neuropsychiatric and rehabilitative services towards psychiatric and community-based services. The rise in prevalence – based on administrative data – of ASD in children might lead to a large number of adolescents who will be entering the young adult's healthcare system in the future and will require specific support. More studies are needed to investigate the actual needs of ASD patients in order to plan future public healthcare policies and interventions.

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Contributors: ST, AGR, and MB conceived and devised the study, and ST analysed the data. All authors contributed to the interpretation of the data. ST drafted the article and AGR reviewed and edited the manuscript, and approved the version to be published, and agree to be accountable for all aspects of the work. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. ST and AGR accept full responsibility for the work and the conduct of the study, had access to the data, and controlled the decision to publish.

Compliance with Ethical Standards : The data are administrative ones, so no informed consent was necessary. The Agency of Health Protection has among its institutional functions, established by the Lombardy Region legislation, the evaluation of the care pathways of autistic patients transitioning to adulthood (DRG 7600, 20 Dec 2017, available at http://www.regione.lombardia.it/wps/wcm/connect/cf479d70-9c53-4491-b5b7-0a6d43fdcd43/DGR2017_7600_regole_2018.pdf?MOD=AJPERES&CACHEID=cf479d70-9c53-4491-b5b7-0a6d43fdcd43, page 68), which is considered a critical element to monitor at present in the Regional and National Italian Health System. Therefore, the Agency of Health Protection of Milan is allowed to use the anonymized administrative data to perform the evaluation of the services provided to autistic patients residing in the covered area. Patient identity was masked by anonymization according to the standard ISO 25237:201. Their unique identification number (fiscal code) was transcoded into a string by the Information System of the Agency of Health Protection, which had no role in analysing the data.

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Competing interests: None declared.

Data sharing statement: The administrative data used for the present study contain sensitive information of underage people. Even though data have been anonymised we will not be able to share your data with other researchers.

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Table 1. Demographics characteristic of ASD patients at 18th years old

Calendar years of recruitment	ASD patient	Gender		Quintile of Deprivation Index					
	N. (%)	*Female % (N.)*	*Male % (N.)*	*I more rich*	*II*	*III*	*IV*	*V more poor*	*missing*
2012	69 (20.85%)	20.29% (14)	79.71% (55)	11.59% (8)	15.94% (11)	23.19% (16)	27.54% (19)	20.29% (14)	1.4% (1)
2013	75 (22.66%)	12.00% (9)	88.00% (66)	5.33% (4)	24.00% (18)	17.33% (13)	28.00% (21)	25.33% (19)	0%(0)
2014	92 (27.79%)	31.52% (29)	68.48% (63)	16.30% (15)	18.48% (17)	25.00% (23)	27.17% (25)	11.96% (11)	1%(1)
2015	95 (28.70%)	23.16% (22)	76.84% (73)	10.53% (10)	22.11% (21)	22.11% (21)	20.00% (19)	24.21% (23)	1%(1)
All	331	22.36% (74)	77.64% (257)	11.18% (37)	20.24% (67)	22.05% (73)	25.38% (84)	20.24% (67)	0.9%(3)

Table 2. Distribution of other psychiatric diagnosis and co-occurring condition by age and regression model output

	Age (years) % (N.)					Age as categorical OR (95%CI)					Age as continuous OR (95%CI)	
Conditions	**16**	**17**	**18**	**19**	**20**	**Female vs Male**	**16 vs 18**	**17 vs 18**	**19 vs 18**	**20 vs 18**	**Female vs Male**	**Age effect**
ALL CO-OCCURRING CONDITION (epilepsy included)	22.4% (74)	20.2% (67)	21.8% (72)	20.8% (69)	21.8% (72)	0.86 (0.51-1.45)	1.04 (0.83-1.29)	0.91 (0.71-1.16)	0.93 (0.77-1.12)	0.98 (0.79-1.22)	0.89 (0.53-1.50)	0.99 (0.93-1.05)
Only Epilepsy	9.1% (30)	8.2% (27)	10.3% (34)	10% (33)	9.7% (32)	0.92 (0.45-1.90)	0.87 (0.65-1.16)	0.79 (0.58-1.08)	0.97 (0.78-1.20)	0.90 (0.71-1.15)	1.01 (0.49-2.08)	1.01 (0.93-1.10)
PSYCHIATRIC DIAGNOSIS	42.6% (141)	50.8% (168)	59.8% (198)	63.7% (211)	66.5% (220)	2.06 (1.27-3.33)	0.48 (0.41-0.58)	0.68 (0.58-0.77)	1.19 (1.09-1.31)	1.36 (1.20-1.53)	2.08 (1.29-3.36)	1.30 (1.23-1.37)
F00-F09: Organic, including symptomatic, mental disorders	0.9% (3)	1.8% (6)	3.3% (11)	4.2% (14)	4.8% (16)	1.68 (0.53-5.26)	0.26 (0.10-0.70)	0.52 (0.21-1.92)	1.29 (0.97-1.71)	1.48 (1.05-2.09)	1.82 (0.60-5.54)	1.41 (1.21-1.64)
F20-F29: Schizophrenia, schizotypal and delusional disorders	11.2% (37)	16.9% (56)	20.8% (69)	23.9% (79)	26.3% (87)	1.37 (0.77-2.44)	0.47 (0.36-0.61)	0.68 (0.51-0.88)	1.20 (1.07-1.33)	1.37 (1.19-1.57)	1.33 (0.75-2.35)	1.27 (1.20-1.36)
F30-F39: Mood [affective] disorders	2.7% (9)	6.3% (21)	8.5% (8)	10.6% (35)	13.3% (44)	3.25 (1.62-6.50)	0.29 (0.17-0.51)	0.74 (0.57-1.91)	1.29 (1.07-1.55)	1.69 (1.32-2.16)	3.14 (1.61-6.14)	1.43 (1.30-1.59)
F40-F48: Neurotic, stress-related and somatoform disorders	6.9% (23)	10.6% (35)	13.6% (45)	16.9% (56)	19.3% (64)	1.46 (0.77-2.78)	0.48 (0.35-0.65)	0.71 (0.62-2.89)	1.31 (1.12-1.53)	1.55 (1.28-1.88)	1.44 (0.76-2.72)	1.31 (1.21-1.42)
F60-F69: Disorders of adult personality and behaviour	5.7% (19)	9.1% (30)	13.3% (44)	16.9% (56)	18.7% (62)	2.28 (1.23-4.25)	0.39 (0.26-0.57)	0.67 (0.51-0.80)	1.34 (1.14-1.58)	1.53 (1.26-1.84)	2.14 (1.16-3.94)	1.35 (1.25-1.47)
F70-F79: Mental retardation	26.9% (89)	29.9% (99)	35% (116)	37.2% (123)	39% (129)	1.52 (0.92-2.52)	0.68 (0.59-0.78)	0.72 (0.71-0.88)	1.10 (1.02-1.18)	1.19 (1.08-1.30)	1.52 (0.92-2.51)	1.15 (1.10-1.20)
F90-F98: Behavioural and emotional disorders with onset usually occurring in childhood and adolescence	10.6% (35)	11.2% (37)	12.7% (42)	14.2% (47)	15.4% (51)	1.01 (0.48-2.11)	0.81 (0.70-0.95)	0.86 (0.76-0.98)	1.11 (1.00-1.23)	1.23 (1.07-1.41)	1.01 (0.49-2.12)	1.11 (1.05-1.17)

Table 3. Analysis of the access to health / social services in ASD patients and Odds ratio (OR) and corresponding confidence intervals from logistic regression

	Age (years) % (N.)					Female vs Male	Age as categorical OR (95%CI)				Age as continuous OR (95%CI)	
	16	17	18	19	20		16 vs 18	17 vs 18	19 vs 18	20 vs 18	Female vs Male	Age effect
Global access	46.5% (154)	58.6% (194)	68% (225)	57.4% (190)	54.1% (179)	1.40 (0.95-2.07)	0.47 (0.35-0.64)	0.73 (0.56-0.96)	0.55 (0.42-0.72)	0.44 (0.33-0.59)	1.36 (0.92-2)	0.97 (0.9-1.06)
Visit neuropsychiatry as outpatient	15.4% (51)	25.1% (83)	30.8% (102)	10% (33)	5.4% (18)	1.19 (0.77-1.85)	0.47 0.34-0.67)	0.79 (0.59-1.07)	0.25 (0.17-0.36)	0.12 (0.07-0.20)	1.15 (0.76-1.74)	0.76 (0.69-0.84)
Visit Neurology as outpatient	4.5% (15)	3.3% (11)	4.8% (16)	6.6% (22)	10.6% (35)	1.66 (0.87-3.19)	1.11 (0.55-2.22)	0.78 (0.38-1.60)	1.47 (0.83-2.61)	2.52 (1.45-4.38)	1.68 (0.87-3.22)	1.29 (1.10-1.53)
Visit Psychiatry as outpatient	12.7% (42)	10% (33)	13.6% (45)	13.6% (45)	14.8% (49)	0.95 (0.64-1.41)	0.97 (0.62-1.50)	0.75 (0.48-1.19)	1.01 (0.65-1.57)	1.07 (0.70-1.64)	0.94 (0.64-1.40)	1.05 (0.94-1.17)
Test as outpatient	6.6% (22)	6.6% (22)	8.5% (28)	3% (10)	1.8% (6)	1.05 (0.59-1.87)	0.78 (0.42-1.46)	0.78 (0.45-1.33)	0.33 (0.16-0.71)	0.2 (0.08-0.46)	1.06 (0.60-1.87)	0.76 (0.65-0.87)
Rehabilitation as outpatient	19.9% (66)	20.2% (67)	16.9% (56)	3.9% (13)	3.9% (13)	1.09 (0.65-1.83)	1.38 (0.97-1.96)	1.33 (0.99-1.79)	0.2 (0.11-0.35)	0.19 (0.11-0.34)	1.09 (0.65-1.81)	0.62 (0.56-0.69)
Psychological support as outpatient	15.1% (50)	13.3% (44)	12.1% (40)	6.3% (21)	3.3% (11)	1.74 (1.02-2.98)	1.37 (0.95-1.98)	1.18 (0.81-1.73)	0.47 (0.3-0.73)	0.25 (0.13-0.48)	1.74 (1.02-2.98)	1.37 (0.95-1.98)
ED access[a]	19.3% (64)	22.7% (75)	23.3% (77)	21.5% (71)	19% (63)	1.22 (0.82-1.81)	0.91 (0.64-1.28)	1.03 (0.73-1.44)	0.86 (0.62-1.20)	0.72 (0.51-1.01)	1.22 (0.82-1.81)	0.94 (0.86-1.02)
CMHS	0% (0)	0.9% (3)	15.1% (50)	19.3% (64)	20.8% (69)	0.9 (0.5-1.63)	-	-	1.27 (0.97-1.66)	1.33 (0.99-1.78)	0.88 (0.49-1.6)	1.15 (0.99-1.32)
Rehabilitation	17.8% (59)	13.3% (44)	11.5% (38)	4.8% (16)	1.8% (6)	1.33 (0.73-2.43)	1.77 (1.35-2.33)	1.22 (1.02-1.45)	0.38 (0.25-0.59)	0.14 (0.06-0.30)	1.43 (0.79-2.59)	0.61 (0.54-0.68)
Psychiatry visits outpatient and CMHS	12.7% (42)	10.3% (34)	17.8% (59)	23.6% (78)	25.4% (84)	1 (0.66-1.52)	0.78 (0.52-1.16)	0.57 (0.37-0.86)	1.39 (1.02-1.9)	1.48 (1.08-2.02)	0.99 (0.65-1.5)	1.22 (1.11-1.35)
Hospital admission	16.9% (56)	22.4% (74)	16.9% (56)	19.3% (64)	16% (53)	1.12 (0.75-1.66)	1.42 (0.98-2.05)	1.80 (1.25-2.59)	1.11 (0.78-1.59)	0.82 (0.54-1.23)	1.12 (0.75-1.66)	0.86 (0.78-0.94)
Psychiatry ward	1.2% (4)	2.7% (9)	5.7% (19)	8.5% (28)	6.3% (21)	1.24 (0.68-2.28)	0.29 (0.1-0.79)	0.54 (0.26-1.12)	1.44 (0.89-2.33)	0.97 (0.54-1.74)	1.26 (0.69-2.29)	1.28 (1.1-1.49)
Neuropsychiatry ward	8.8% (29)	10.3% (34)	4.5% (15)	0.9% (3)	0.3% (1)	1.89 (0.97-3.7)	3.18 (1.77-5.72)	3.19 (1.84-5.52)	0.18 (0.05-0.59)	0.06 (0.01-0.38)	1.96 (1-3.84)	0.44 (0.38-0.51)
Psychiatry and neuropsychiatry ward	9.4% (31)	10.6% (35)	9.4% (31)	9.4% (31)	6.6% (22)	1.40 (0.85-2.31)	1.48 (0.92-2.40)	1.43 (0.92-2.22)	0.93 (0.59-1.47)	0.59 (0.35-1.01)	1.41 (0.86-2.32)	0.80 (0.7-0.91)
Residential facility	6.6% (22)	6.3% (21)	8.8% (29)	7.3% (24)	6% (20)	0.97 (0.45-2.05)	0.82 (0.52-1.30)	0.76 (0.53-1.10)	0.77 (0.54-1.09)	0.66 (0.43-1.01)	1.00 (0.47-2.13)	0.95 (0.81-1.10)
CSS	4.8% (9)[a]	11.1% (29)[a]	18.4% (61)	20.5% (68)	21.8% (72)	1.46 (0.78-2.74)	0.20 (0.1-0.41)	0.51 (0.37-0.7)	1.15 (1-1.32)	1.21 (1.02-1.45)	1.49 (0.81-2.73)	1.33 (1.22-1.45)

[a] Since databases started from 2012 as denominator we included only contributing age after 2012

(Cont'd)

Table 3. (Continue) Analysis of the access to health / social services in ASD patients and Odds ratio (OR) and corresponding confidence intervals from logistic regression

	Age (years) % (N.)						Age as categorical OR (95%CI)				Age as continuous OR (95%CI)	
	16	17	18	19	20	Female vs Male	16 vs 18	17 vs 18	19 vs 18	20 vs 18	Female vs Male	Age effect
All neuroleptic prescriptions [b]	35.6% (118)	39.3% (130)	44.7% (148)	45% (149)	44.1% (146)	1.18 (0.74-1.88)	0.91 (0.74-1.14)	0.93 (0.78-1.10)	0.94 (0.78-1.13)	0.85 (0.68-1.07)	1.18 (0.74-1.89)	0.98 (0.92-1.05)
Antidepressant (N06A)	5.7% (19)	7.9% (26)	10.6% (35)	9.4% (31)	11.2% (37)	2.54 (1.40-4.64)	0.63 (0.40-0.98)	0.78 (0.54-1.15)	0.81 (0.58-1.15)	0.99 (0.66-1.50)	2.50 (1.37-4.55)	1.10 (0.98-1.24)
Antipsychotic (N05)	27.8% (92)	30.8% (102)	33.8% (112)	34.1% (113)	34.7% (115)	0.57 (0.34-0.96)	1.04 (0.72-1.49)	1.01 (0.75-1.36)	0.92 (0.69-1.22)	0.91 (0.65-1.27)	0.57 (0.34-0.96)	0.97 (0.87-1.07)
Anxiolytic (N05B, N05CD, N05CF)	0.9% (3)	1.8% (6)	1.5% (5)	1.5% (5)	1.5% (5)	3.63 (0.84-15.61)	0.70 (0.24-2.04)	1.48 (0.76-2.85)	0.91 (0.34-2.42)	1.06 (0.43-2.66)	6.00 (1.37-26.24)	1.06 (0.80-1.41)
Antiepileptic (NO3A)	16.3% (54)	16.3% (54)	20.8% (69)	23.0% (76)	23.9% (79)	1.22 (0.71-2.08)	0.91 (0.72-1.16)	0.84 (0.68-1.03)	1.11 (0.92-1.34)	1.13 (0.90-1.41)	1.22 (0.72-2.08)	1.06 (0.99-1.13)
AHDH prescriptions (NO6BA)	0.6% (2)	0.6% (2)	0.6% (2)	0% (0)	0.3% (1)							
Risperidone and/or Aripiprazole (N05AX08, N05AX12)	20.2% (67)	21.8% (72)	23.6% (78)	25.4% (84)	24.2% (80)	0.82 (0.49-1.36)	1.14 (0.86-1.52)	1.09 (0.87-1.36)	1.08 (0.89-1.31)	0.97 (0.76-1.23)	0.81 (0.48-1.34)	0.96 (0.89-1.04)
Risperidone (N05AX08)	15.7% (52)	15.4% (51)	15.7% (52)	15.4% (51)	15.4% (51)	0.54 (0.31-0.94)	1.32 (0.97-1.80)	1.15 (0.89-1.48)	0.93 (0.72-1.20)	0.90 (0.67-1.20)	0.54 (0.31-0.94)	0.91 (0.83-0.99)
Aripiprazole (N05AX12)	5.1% (17)	8.5% (28)	10.3% (34)	11.5% (38)	10.9% (36)	1.47 (0.74-2.92)	0.66 (0.40-1.08)	0.99 (0.70-1.40)	1.14 (0.86-1.50)	1.04 (0.73-1.50)	1.47 (0.73-2.94)	1.09 (0.97-1.24)
Valproic acid (N03AG01)	12.7% (42)	10.9% (36)	15.4% (51)	16.3% (54)	18.1% (60)	1.02 (0.54-1.92)	1.01 (0.77-1.33)	0.77 (0.58-1.02)	1.04 (0.84-1.30)	1.15 (0.88-1.49)	1.02 (0.55-1.88)	1.04 (0.96-1.13)

[b] ATC code "N" (nervous system) excluding anaesthetics (N01) and analgesics (N02)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3/4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	-
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*6-8*
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	-
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7-8
		(*b*) Describe any methods used to examine subgroups and interactions	7-8
		(*c*) Explain how missing data were addressed	-
		(*d*) If applicable, explain how loss to follow-up was addressed	-
		(*e*) Describe any sensitivity analyses	-
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	-
		(c) Consider use of a flow diagram	-
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8;22
		(b) Indicate number of participants with missing data for each variable of interest	22
		(c) Summarise follow-up time (eg, average and total amount)	-
Outcome data	15*	Report numbers of outcome events or summary measures over time	8-10; 23-25
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	-
		(*b*) Report category boundaries when continuous variables were categorized	-
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	-
Discussion			
Key results	18	Summarise key results with reference to study objectives	15
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14-15
Generalisability	21	Discuss the generalisability (external validity) of the study results	14-15
Other information			12
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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DO AUTISTIC PATIENTS CHANGE HEALTHCARE SERVICES UTILIZATION THROUGH THE TRANSITION-AGE? AN ITALIAN LONGITUDINAL RETROSPECTIVE STUDY

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DO AUTISTIC PATIENTS CHANGE HEALTHCARE SERVICES UTILIZATION THROUGH THE TRANSITION-AGE? AN ITALIAN LONGITUDINAL RETROSPECTIVE STUDY

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Keywords: Autism spectrum disorder; Epidemiology; Administrative databases; Health outcomes; Health service research

DO AUTISTIC PATIENTS CHANGE HEALTHCARE SERVICES UTILIZATION THROUGH THE TRANSITION-AGE? AN ITALIAN LONGITUDINAL RETROSPECTIVE STUDY

ABSTRACT

Objectives: This paper aims to provide an estimate of the prevalence rate of autism spectrum disorder (ASD) in 8-year-olds in 2017 based on administrative databases and to investigate the change in healthcare service use during the healthcare transition age of 18.

Design: This research is based on a longitudinal retrospective cohort study.

Setting: The data is drawn from the Italian Administrative Healthcare Database (2010-2017).

Participants: We identified 5,607 ASD patients; 331 ASD patients from 2012 to 2015 in the calendar year of their 18th birthday were selected and their health service utilization during a 5-year period—ranging from two years preceding and succeeding their 18th year—were investigated.

Interventions: none

Primary and secondary outcome measures: Prevalence, incidence, and proportion of ASD patients receiving specific healthcare services were included in the outcome measures.

Results: Prevalence of ASD at age 8 was 5.4/1,000. Global access to health and social services was lower both before and after age 18 (46.5% at 16; 68% at 18; 54.1% at 20). The percentage of patients receiving a neuropsychiatric consultation decreased after age 18 (30.8% at 18; 5.4% at 20). Community mental health services (CMHS) utilization rate increased above 18 years of age. Regarding psychiatric visits, for both outpatient and CMHS services, an increase was observed from 17.8% at age 18 to 25.4% at age 20. The utilization of rehabilitation services decreased with age, dropping from 17.8% at age 16 to 1.8% at age 20. Psychiatric outpatient services remained stable across ages at about 14%.

Conclusions: Our findings suggest that ASD patients changed clinical reference services with age from neuropsychiatric and rehabilitative services towards psychiatric and community-based services as they transitioned from pediatric to adult healthcare services.

Keywords: Autism spectrum disorder; Epidemiology; Administrative databases; Health outcomes; Health service research

Strengths and limitations of this study

- Longitudinal retrospective cohort study based on Administrative Healthcare Database: real-world diagnostic patterns of a large and unselected population (3.5 million habitants)
- Estimation of prevalence and incidence rates, differences in comorbidity, and healthcare services utilization in an unselected retrospective longitudinal cohort of ASD patients from 16 to 20 years of age
- Diagnosis codes and healthcare services utilization based only on the administrative data

INTRODUCTION

Autism spectrum disorder (ASD) is a brain-based chronic neurodevelopmental disorder with lifelong impacts. It is characterized and diagnosed by impairments in social communication and social interaction with the presence of restricted, repetitive behaviors [1]. Onset of ASD typically occurs by age 3, although some studies suggest that symptoms can emerge between 6 and 18 months of age and may not be fully manifested until school age [2,3]. Children, adolescents, and adults with ASD can often present a number of comorbidities including psychiatric conditions, intellectual disabilities, developmental delay, epilepsy, anxiety, language and motor difficulties, and depression [4–7].

The etiology of ASD remains largely unexplained. It seems to be highly heritable [8], and some environmental risk factors [9] and parental age [10] may be involved. The prevalence of ASD has increased in the last decades, although the reasons for this increase are not fully understood. It might be related to etiologic, non-etiologic, and administrative factors (e.g. modified diagnostic criteria, improved access to services, and increased public and scientific interest [6,11,12]).

A review published in 2012 [13] estimated the global prevalence of ASD to be about 1% (62/10000); a more recent study has estimated the prevalence to be 1.5% in developed countries [14–16]. In 2014 [15], a prevalence rate of 16.8 per 1000 was estimated for children aged 8.

Treatments for ASD vary across the world and even within country regions, and it has been reported that parents with a lower educational level are less successful in obtaining specialist interventions that could improve outcomes [6]. Treatments for ASD include early parent-mediated interventions and behavioral and social treatments. Evidence-based pharmacology in ASD is currently limited to the treatment of co-occurring behaviors or diagnoses, not ASD itself [6]. Risperidone [17] and aripiprazole [18] have improved symptoms

of irritability or agitation in children and adolescents with ASD. Methylphenidate [19], atomoxetine [20], and guanfacine [21] have shown a benefit for ADHD symptoms in ASD. However, the use of such drugs presents some adverse effects, and their use has been indicated for a specific age period.

While autism is generally considered a disorder of childhood, the rise in ASD prevalence in the last decades has produced an increase of individuals with ASD transitioning from pediatric to young adult medical services resulting in autism rapidly becoming a disorder of adulthood as well [22]. There is evidence that for young people with special healthcare needs, such as autism, transitioning form pediatric to adult healthcare can be problematic [23,24]. The transition process may be especially difficult for young people whose special healthcare needs involve mental health, developmental disabilities, or intellectual disabilities [24]. Moreover, the lack of ASD treatment guidelines for adult patients increases the complexity of healthcare delivery and involves a complicated transition from pediatric to adult healthcare [25]. Very often, the transition to adulthood in people with ASD results in poor outcomes across multiple domains including employment, education, healthcare, social engagement, and independent living [26,27], even in the presence of targeted healthcare transition services [28]. This may represent problems both for parents [27] and patients [29].

Often the transition from the pediatric to the adult healthcare system coincides with an exit from the educational system (i.e. high school) where adolescents may receive daily support that further affects service usage. However, to our knowledge, only a few studies have described changes in healthcare service usage during the transition to adulthood in people with ASD [24,26,30]. Administrative claims data can be plentiful, comprehensive, cost efficient, and free from some of the biases that accompany other types of data, such as surveys or self-reports [31]. Analyses of administrative healthcare databases have the potential to include a large number of individuals and have been successfully used in the study of health outcomes associated with a

variety of conditions [31,32]. Studies conducted in the US [33] and Canada [34,35] have indicated that administrative claims data were able to clearly identify children with ASD.

The purpose of this paper is to provide an estimate of the prevalence of ASD at 8 years of age using administrative databases derived from the largest Northern Italian population. Further, this study investigated the change in healthcare services use during the transition from the pediatric to young adult healthcare systems.

METHODS

Data collection

A retrospective cohort study was conducted using the Administrative Healthcare Database of the Agency for Health Protection of Milan (AHD-ATS) from January 1, 2010 to December 31, 2017. Only data regarding patients residing in the ATS were considered. In Italy, the National Healthcare System (NHS) is universal and fully covers the population and the ATS provides care to about 3,500,000 inhabitants.

Data were obtained from AHD-ATS, which included eight different databases: 1) outpatient activity data (6 million (M) records), such as visits and tests performed by residents in the study area in ambulatories and laboratories; 2) hospital discharge records (1 M); 3) co-payment Exemption Register (1 M); 4) emergency department (ED) visits (2 M); 5) rehabilitation interventions database (800,000), such as visits and rehabilitative therapy (i.e. speech therapy, physiotherapy, and educative and occupational therapy); 6) community mental health services (CMHS) (100,000) such as psychiatry visits, residential facilities, pharmacological interventions, and family support in psychiatric setting; 7) pharmaceutical prescription database (200 M); and 8) community and social services (CSS) (1 M) such as family support, day care centers, community and residential facilities, home care, home care economic aid, and hospice.

Demographic information was obtained by record linkage using a unique identifier code with patients' master data and Deprivation Index by using record linkage with the 2001 General Census of Population and Housing.

ASD patients were defined as individuals having a reported diagnosis of ASD (ICD-9 codes 299.00 to 299.99 or their ICD-10 equivalents) in at least one of the databases during the study period [35]. For each patient, the calendar year of birth was used as an approximate age value at the time of service utilization.

Statistical analysis

Prevalence and incidence rates estimation

Prevalence rates were estimated for 2017 at age 8 and incidence rates ranging from 2-8 years of age, based on administrative databases. The prevalence rate was obtained by dividing the number of children 8 years old diagnosed with ASD in 2017 or previously, by the population size—of the same age—in the study area as of 1 January 2018, based on the Italian National Institute of Statistics.

The annual incidence rates were obtained by dividing the annual number of children aged 2-8 years, newly diagnosed, by the general population and subtracting the number of ASD diagnoses in preceding years. Binomial 95% confidence intervals (95% CI) were calculated for the prevalence and incidence rates.

Consumptions and outcome models

We selected ASD patients from 2012 to 2015 in the calendar year of their 18th birthday, and we investigated health services utilization during a 5-year period: the four years bracketing their 18th year and the 18th year (i.e. aged from 16 to 20). We investigated the percentage of co-occurring conditions related to other psychiatric diseases; as an outcome variable, we investigated access to services (i.e. outpatient, rehabilitation interventions, community/social services, ED access, hospital admissions, and neuroleptic drug consumption).

Co-occurring conditions were identified using the chronicity database [36] that covers the 13 main comorbidity conditions (hypertension, diabetes, dyslipidemia, COPD, heart failure, renal failure, neoplasms, cardiovascular diseases, inflammatory bowel disease, chronic liver diseases, chronic neurological diseases, autoimmune diseases, and endocrine and metabolic diseases). The proportion of ASD patients with a co-occurring psychiatric diagnosis was estimated by searching for psychiatric diagnoses (ICD-10 code: F00 to F99 with F84, autistic disorder, excluded and their ICD-9 conversion according to the database encoding) in the AHD-ATS databases; we assumed that the psychiatric conditions persisted over time after the first psychiatric diagnoses were recorded.

As outcomes, we investigated consumption of outpatient services (psychiatric, neurologic, and neuropsychiatric visits; tests and psychological services), ED admissions, rehabilitation interventions, CMHS interventions, hospital admissions (psychiatry and neuropsychiatric hospitalization), residential services, and CSS utilizations.

With regard to neuroleptic drug consumption, we investigated the percentages of ASD patients who had at least one prescription for any psychotropic substances according to the anatomical therapeutic chemical (ATC) classification. We selected all substances with ATC code "N" (nervous system) excluding anesthetics (N01) and analgesics (N02). In addition, we included antidepressants (N06A), antipsychotics (N05), anxiolytics/tranquilizers (N05B, N05CD, N05CF), ADHD medication (N06BA), and antiepileptics (N03A) as separate groups. Risperidone (N05AX08), aripiprazole (N05AX12), and valproic acid (N03AX09) consumption were also considered.

The binary responses of co-occurring diseases, other psychiatric diagnoses, service consumptions, and outcomes at ages 16-20 were modelled by repeated measurements using a generalized estimating equation (GEE) approach with a dichotomic response variable. The binary responses for individual ASD patients were assumed to be equally correlated; thus, an

exchangeable correlation structure was assumed. Ages were modelled first as a categorical variable with age 18 as reference. Regressions for co-occurring diseases and other psychiatric diagnoses were adjusted by a gender and deprivation index; in addition, logistic regressions for service consumption and outcomes were adjusted for co-occurring diseases and other psychiatric diagnoses.

Patient and public involvement

Neither patients nor the public were involved in the design or conduct of this study.

RESULTS

During the period between 2010 and 2017, we identified 5,607 patients (4,109 male and 1,498 female) who met the inclusion criteria. Mean age as of 2017 was 22 years (ranging from 1-90), 19 years old for males (1-88) and 30 years for females (2-90). Based on administrative data, the prevalence of ASD at 8 years old on 31 December 2017 was 5.4/1,000 inhabitants (95% CI 4.6-6.2); prevalence for males was about three times that of females; 8.1/1,000 (95% CI 6.8-9.5) for males and 2.6/1,000 inhabitants (95 % CI 1.8-3.5) for females. The incidence rate for 2-8 years in 2017 was 2.1 per 1,000 inhabitants/year (95% CI 1.9-2.3). Incidence in males was higher than in females: 3.3 (95% CI 1.9-2.3) for males and 0.8 per 1,000 inhabitants/year (95% CI 0.6-0.9) for females.

We included all patients (331) who were 18 years old between 2012 and 2015 (Table 1), of whom 257 (77.64%) were male and 74 (22.36%) were female. Regarding the deprivation index, at 18 years of age, 11.18% were in the least deprived quintile, while 20.24% were in the most deprived quintile; no differences were found in the quintile distribution by calendar year ($p = 0.2$).

Co-occurring conditions (Table 2) were present in about 22% of patients at 16 years of age and remained constant among ages; no differences were found for gender or deprivation index. In contrast, other psychiatric diagnoses increased from 42.6% at 16 years of age to 66.5%

at age 18 ($p < 0.001$); females had a greater risk than males ($p = 0.003$), and no differences were found for the deprivation index.

The most reported psychiatric condition was mental retardation (F70-F79) at over 30%; schizophrenia, schizotypal, and delusional disorders (F20-F29) were over 20%; anxiety, dissociative, stress-related, somatoform, and other nonpsychotic mental disorders (F40-F48) were about 20%. Behavioral and emotional disorders F90-F98 reached 15.4%.

Schizotypal and delusional disorders increased from 11.2% at 16 years old to 26.3% at age 18 ($p = 0.001$); at 16 years old about 30% of individuals with ASD had intellectual disabilities, and that percentage increased with age reaching 39% at 20 years ($p < 0.001$). We found a greater risk for females regarding mood affecting disorders (F30-F39, $p < 0.001$) and disorders of adult personality and behavior (F60-F69, $p = 0.009$).

The percentage of ASD patients with at least one instance of access to health services by age is reported in Table 3. Global access to health and social services are lower both before and after age 18 (Table 3), with comparable levels at 16 and 20 years of age ($p = 0.08$).

The percentage of patients receiving a neuropsychiatric consultation (Table 3) decreases after 18 years of age (from 30.8% at age 18 to 5.4% at age 20; OR = 0.12; 95% CI 0.07-0.32). However, neurologist visits increase after 18 years of age (4.9% at age 18 to 10.6% at 20; OR = 2.52; 95% CI 1.45-4.38) and only at 20 years of age reach statistical significance compared to age 18. Psychiatric outpatient visits remained stable across all ages (14%). Outpatient healthcare services showed a statistically significant decrease after 18 years of age: psychological services (from 15.1% at age 18 to 3.3% at age 20; $OR_{20vs18} = 0.25$; 95% CI 0.13-0.48); rehabilitative services (from 19.9% to 3.9%; $OR_{20vs18} = 0.19$; 95% CI 0.11-0.34); and tests (from 6.6% to 1.8%; $OR_{20vs18} = 0.20$; 95% CI 0.08-0.46). The ED admission figure showed a significant increase from 16 years of age (19.3%) to age 18 (23.3%, $OR_{16vs18} = 0.91$; 95% CI 0.64-1.28) and then decreased to 19% ($OR_{20vs18} = 0.72$; 95% CI 0.52-1.01) at age 20.

As CMHS usually treats adult patients, access to this service was investigated starting from 18 years of age. No access to CMHS was recorded before age 18, and an increase in the utilization rate was found over age 18 (from 15.1% at age 18 to 20.8% at age 20; OR_{20vs18} = 1.33; 95% CI 0.99-1.78). For psychiatric visits, both in outpatient services and CMHS, a rate increase was observed after 18 years of age, from 17.8% at age 18 to 25.4% at age 20 (OR_{20vs18} = 1.48; 95% CI 1.08-2.02). The utilization of rehabilitation services decreased with age—from 17.8% at age 18 to 1.8% at age 20 (OR_{20vs18} = 0.38; 95% CI 0.25-0.59).

Global hospital admissions decreased with age, with a significant decrease at 18 years of age compared to age 17 (from 22.4% at age 17 to 16.9% at age 18; OR_{17vs18} = 1.80; 95% CI 1.25-2.59). Neuropsychiatric and psychiatric hospital admissions showed opposite trends: neuropsychiatric accesses decreased with age (from 8.8% at age 18 to 0.3% at age 20; OR_{20vs18} = 0.06; 95% CI 0.01-0.38) while psychiatric accesses increased (from 1.2% at age 18 to 6.3% at age 20; OR_{20vs18} = 0.97; 95% CI 0.54-1.74). It should be noted that neuropsychiatric and psychiatric hospital admissions together remained stable across ages (9.4% at age 16 to 6.6% at age 20; OR_{20vs18} = 0.59; 95% CI 0.35-1.01).

More than 40% of ASD patients had neurological drug prescriptions, and the percentage increased with age; however, the increase was not statistically significant. Antipsychotics (about 30%) and antiepileptics (about 20%) were the most commonly prescribed drugs, and these percentages did not show a statistically significant increase with age. In detail, risperidone (15%) and aripiprazole (from 5% to 11.5%) were the antipsychotics drugs most frequently prescribed. Valproic acid was the most frequent epileptic drug prescribed (about 20% of ASD patients); no statistically significant differences were found across ages.

DISCUSSION

Autism is a major topic in public health debates and between the initial diagnosis and the age of 18, the Italian healthcare system provides an efficient management model based on child neuropsychiatry. Child neuropsychiatry is devoted to neurological, behavioral, emotional, and psychiatric disorders in childhood and adolescence while psychiatry units usually are devoted only to psychiatric disorders, particularly in adulthood. The results from this study, based on the innovative and integrated use of healthcare and social databases, show that, in the transition to adulthood, there is a change in the models used in taking care of a child diagnosed with autism.

The use of administrative databases allowed us to study real-word diagnostic patterns of a large and unselected population. However, the diagnoses used in this analysis were made by physicians specialized in a variety of disciplines, which may lead to diagnostic imprecision. Indeed, the estimated prevalence of ASD at 8 years of age (0.54%) is lower than the autism prevalence of 1.68% reported by the most recent study [15]. Nevertheless, our estimate is very close to a value estimated in less recent years [37–39]. It is also similar to the prevalence reported using administrative databases in Germany during 2012 [40] for age groups ranging from 6 to 11 years (0.6%) and in France (0.35%) from register-based data [41]. In Italy, few studies reporting autism prevalence have been carried out; in a recent paper, Narzisi et al. [42] estimated a prevalence of 0.8% in children aged 7-9. This figure is higher than ours, but the different study setting might have influenced the results, as Narzisi et al. based theirs on a sample extracted at the community level. However, if we considered only children included in Narzisi et al. with both certified disability and ASD, a prevalence of 0.65% would be assessed—much closer to our estimate. Since ASD is generally diagnosed after 1 year of age and our data started from 2010, we believe that only a small number of ASD-diagnosed patients who were 8 years old in 2017 were not included. Our underestimation of ASD may be due to a number of reasons: 1) a delayed diagnosis after 8 years old; 2) a lack of recorded diagnosis in

administrative databases; 3) a limited tendency to register the autism diagnosis in Lombardy by physicians; 4) a misclassification of the diagnosis; or 5) only more serious cases were diagnosed by physicians of the NHS.

With respect to incidence, we estimated for 2017 an annual incidence rate—based on administrative databases—of about 2/1000 for children aged 2-8, but we were able to find only one study for comparison [37], which estimated an annual incidence of 1.02/1000 in boys and 0.21/1000 in girls aged 2-8. This figure is lower than ours; however, it referred to 2010 and the incidence of ASD in the subsequent years could have increased. Furthermore, we were able to estimate an incidence for children 2-6 years old between 2015 and 2017, and we estimated (data not shown) 4.30/1000 for 2015, 4.70 for 2016, and 7.30 for 2017. This suggests an increasing trend for ASD diagnoses reported in administrative claims that will be reflected in the prevalence of the following years. However, the increase of ASD is more related to administrative changes [12] given that fewer symptoms of autism are now required for diagnosis and that a child with a diagnosis of ASD much more often receives support at school and in the community [43], rather than a factor affecting pathogenesis.

Our study investigated the differences in rates of comorbidity and healthcare services utilization in a retrospective longitudinal cohort of ASD patients from 16 to 20 years old. The ASD cohort used in this study included individuals who had been patients with health/social care services utilization over seven years (from 2010 to 2017). Thus, the findings in this cohort could not be connected to general ASD patients during the transition age but to ASD patients who were included in a health/social services pathway and, perhaps, having more serious conditions. Thus, our findings of a high rate (up to 66.5%) of psychiatric conditions (including mental retardation) were not completely surprising, even if higher than those reported in other studies (34% [44]; 54% [5]; 65% [39]). In detail, the percentage of anxiety previously reported in a previous study [44] was similar (14.4%) to ours (19.3%), as well as depression (9.9% vs

13.3%). The percentage of individuals with epilepsy in our study (9%) is comparable with other studies examining the transition age in ASD [44]. We observed a high percentage of schizophrenia, schizotypal, and delusional disorders (over 20%) compared to other studies (between 8% in adults [5,45,46] and 17% in 22-40 years old [7]). This could be related to a change from child neuropsychiatry services to psychiatry services in the young adult phase where personality disorders may be over-diagnosed. Moreover, it must be considered that the diagnosis of other psychiatric conditions was also based on administrative data and thus may depend, at least in part, on which services and specialists were more involved in each patients' care. Surprisingly, we observed an increasing rate of intellectual disability from 16 years to 20; two possible causes should be considered. On one hand, this trend may be related to the end of the pediatric co-payment exemption at age 18 that previously could overwrite other causes of exemption. On the other hand, the end of compulsory education may cause an increase of intellectual assessment request in order to provide a more specific daily support. In Italy, patients remain in charge of pediatric healthcare services until 18 years of age; however, starting at 16 years of age there may be some overlap in healthcare systems. The results of this study suggest that the type of medical services used for ASD patients changes between 16 and 20 years. Further, comparison between ages showed that general healthcare services utilization increases from 16 to 18 years old and subsequently decreases.

Neuropsychiatric and rehabilitation services decreased with age as ASD patients began treatment with CMHS and CSS; this suggests a change in the care path for these people. Indeed, the percentage of ASD patients with at least one CMHS treatment increased from 18 to 20 years of age. Also, the percentage of ASD patients having psychiatric visits in outpatient care services or CMHS increased from 12.7% at 16 years old to 25.4% at 20 years old. This change in patients' reference services was also confirmed by the decreased rate of ASD patients with neuropsychiatric hospitalization and the corresponding increase of psychiatric hospitalization,

even if globally the hospitalization in dedicated departments (neuropsychiatric or psychiatric) remained stable across ages. This suggests, together with the higher global access observed at age 18, that ASD patients and their families might look for new clinical reference services around the 18th year and then settle down, even if long-term observation may be necessary. In conclusion, we did not observe a decrease in healthcare services utilization as recently reported by Nathenson et al. [30]. Moreover, psychiatric healthcare services may not be the proper type of support considering the special needs (such as speech therapy, rehabilitation, and occupational therapy) of these patients.

The percentage of individuals with ASD who received at least one service related to an ED remains stable with age, although a slight increase in 17-19 year olds was observed. This suggests that even if the clinical reference services changed with age a greater need of the ED was not implied.

Even if the current evidence for the effectiveness of antipsychotic drugs in ASD is only moderate [6], neuroleptic drugs were frequently used in this cohort of ASD patients and their consumption remained stable across ages; moreover, our findings were similar to frequencies reported in other studies [39]. ADHD drugs were less prescribed (less than 0.6%) with respect to other reported prescription rates in ASD patients (about 15%) even considering the patients' age [47]; this may reflect a generally low consumption in Italy of such drugs in childhood [48].

Strengths and Limitations

The current study used large administrative databases, which made it possible to study real-world diagnostic patterns of a large and unselected population without non-responses, interviews, or recall bias issues. However, we must note that we could not include any service utilization outside the NHS. Furthermore, diagnoses in administrative databases are made by physicians specialized in a variety of disciplines and were not validated, which may lead to diagnostic imprecision. In addition, some diagnoses may not have been reported. With regard

to the estimated rate of ASD patients who used healthcare services, we investigated what type of diagnosis these outcomes were associated with and the reasons for such services. However, the CSS and rehabilitation interventions database did not systematically report the type of services provided (i.e. speech therapy, rehabilitation, occupational therapy).

The 16-20 age range provides an opportunity to investigate ASD patients during the transition from pediatric to young adult services, and we were able to follow longitudinally a group of ASD patients in transition age without the birth cohort effect. Unfortunately, our cohort was limited to adolescents with ASD who had had at least one healthcare service contact with a diagnosis code related to ASD starting from 2010; thus, ASD patients who did not use healthcare services during this period would not be included. Accordingly, our findings may not be applied to all ASD patients in transition age but represented ASD patients with some healthcare service connection.

Our study suggested a change in the clinical reference services, but we did not find a reduction in the use of healthcare services with age. However, we were not able to include a survey of caregivers in order to investigate any actual difficulties in managing this transition.

CONCLUSION

Our findings suggest that ASD patients change clinical reference services with age from neuropsychiatric and rehabilitative services towards psychiatric and community-based services. The rise in prevalence, based on administrative data, of ASD in children might lead to a large number of adolescents who will be entering the young adult's healthcare system in the future and will require specific support. More studies are needed to investigate the actual needs of ASD patients in order to plan future public healthcare policies and interventions.

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Contributors: ST, AGR, and MB conceived and devised the study, and ST analysed the data. All authors contributed to the interpretation of the data. ST drafted the article and AGR reviewed and edited the manuscript, and approved the version to be published, and agree to be accountable for all aspects of the work. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. ST and AGR accept full responsibility for the work and the conduct of the study, had access to the data, and controlled the decision to publish.

Compliance with Ethical Standards : The data are administrative ones, so no informed consent was necessary. The Agency of Health Protection has among its institutional functions, established by the Lombardy Region legislation, the evaluation of the care pathways of autistic patients transitioning to adulthood (DRG 7600, 20 Dec 2017, available at http://www.regione.lombardia.it/wps/wcm/connect/cf479d70-9c53-4491-b5b7-0a6d43fdcd43/DGR2017_7600_regole_2018.pdf?MOD=AJPERES&CACHEID=cf479d70-9c53-4491-b5b7-0a6d43fdcd43, page 68), which is considered a critical element to monitor at present in the Regional and National Italian Health System. Therefore, the Agency of Health Protection of Milan is allowed to use the anonymized administrative data to perform the evaluation of the services provided to autistic patients residing in the covered area. Patient identity was masked by anonymization according to the standard ISO 25237:201. Their unique identification number (fiscal code) was transcoded into a string by the Information System of the Agency of Health Protection, which had no role in analysing the data.

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Data sharing statement: The administrative data used for the present study contain sensitive information of underage people. Even though data have been anonymised we will not be able to share your data with other researchers.

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Table 1. Demographics characteristic of ASD patients at 18th years old

Calendar years of recruitment	ASD patient	Gender		Quintile of Deprivation Index					
	N. (%)	*Female % (N.)*	*Male % (N.)*	*I more rich*	*II*	*III*	*IV*	*V more poor*	*missing*
2012	69 (20.85%)	20.29% (14)	79.71% (55)	11.59% (8)	15.94% (11)	23.19% (16)	27.54% (19)	20.29% (14)	1.4% (1)
2013	75 (22.66%)	12.00% (9)	88.00% (66)	5.33% (4)	24.00% (18)	17.33% (13)	28.00% (21)	25.33% (19)	0%(0)
2014	92 (27.79%)	31.52% (29)	68.48% (63)	16.30% (15)	18.48% (17)	25.00% (23)	27.17% (25)	11.96% (11)	1%(1)
2015	95 (28.70%)	23.16% (22)	76.84% (73)	10.53% (10)	22.11% (21)	22.11% (21)	20.00% (19)	24.21% (23)	1%(1)
All	331	22.36% (74)	77.64% (257)	11.18% (37)	20.24% (67)	22.05% (73)	25.38% (84)	20.24% (67)	0.9%(3)

Table 2. Distribution of other psychiatric diagnosis and co-occurring condition by age and regression model output

	Age (years) % (N.)					Age as categorical OR (95%CI)					Age as continuous OR (95%CI)	
Conditions	**16**	**17**	**18**	**19**	**20**	**Female vs Male**	**16 vs 18**	**17 vs 18**	**19 vs 18**	**20 vs 18**	**Female vs Male**	**Age effect**
ALL CO-OCCURRING CONDITION (epilepsy included)	22.4% (74)	20.2% (67)	21.8% (72)	20.8% (69)	21.8% (72)	0.86 (0.51-1.45)	1.04 (0.83-1.29)	(0.91-1.10)	0.93 (0.77-1.12)	0.98 (0.79-1.22)	0.89 (0.53-1.50)	0.99 (0.93-1.05)
Only Epilepsy	9.1% (30)	8.2% (27)	10.3% (34)	10% (33)	9.7% (32)	0.92 (0.45-1.90)	0.87 (0.65-1.16)	(0.68-1.98)	0.97 (0.78-1.20)	0.90 (0.71-1.15)	1.01 (0.49-2.08)	1.01 (0.93-1.10)
PSYCHIATRIC DIAGNOSIS	42.6% (141)	50.8% (168)	59.8% (198)	63.7% (211)	66.5% (220)	2.06 (1.27-3.33)	0.48 (0.41-0.58)	(0.68-0.77)	1.19 (1.09-1.31)	1.36 (1.20-1.53)	2.08 (1.29-3.36)	1.30 (1.23-1.37)
F00-F09: Organic, including symptomatic, mental disorders	0.9% (3)	1.8% (6)	3.3% (11)	4.2% (14)	4.8% (16)	1.68 (0.53-5.26)	0.26 (0.10-0.70)	(0.41-1.92)	1.29 (0.97-1.71)	1.48 (1.05-2.09)	1.82 (0.60-5.54)	1.41 (1.21-1.64)
F20-F29: Schizophrenia, schizotypal and delusional disorders	11.2% (37)	16.9% (56)	20.8% (69)	23.9% (79)	26.3% (87)	1.37 (0.77-2.44)	0.47 (0.36-0.61)	(0.66-1.88)	1.20 (1.07-1.33)	1.37 (1.19-1.57)	1.33 (0.75-2.35)	1.27 (1.20-1.36)
F30-F39: Mood [affective] disorders	2.7% (9)	6.3% (21)	8.5% (8)	10.6% (35)	13.3% (44)	3.25 (1.62-6.50)	0.29 (0.17-0.51)	(0.57-1.91)	1.29 (1.07-1.55)	1.69 (1.32-2.16)	3.14 (1.61-6.14)	1.43 (1.30-1.59)
F40-F48: Neurotic, stress-related and somatoform disorders	6.9% (23)	10.6% (35)	13.6% (45)	16.9% (56)	19.3% (64)	1.46 (0.77-2.78)	0.48 (0.35-0.65)	(0.62-1.89)	1.31 (1.12-1.53)	1.55 (1.28-1.88)	1.44 (0.76-2.72)	1.31 (1.21-1.42)
F60-F69: Disorders of adult personality and behaviour	5.7% (19)	9.1% (30)	13.3% (44)	16.9% (56)	18.7% (62)	2.28 (1.23-4.25)	0.39 (0.26-0.57)	(0.51-1.80)	1.34 (1.14-1.58)	1.53 (1.26-1.84)	2.14 (1.16-3.94)	1.35 (1.25-1.47)
F70-F79: Mental retardation	26.9% (89)	29.9% (99)	35% (116)	37.2% (123)	39.0% (129)	1.52 (0.92-2.52)	0.68 (0.59-0.78)	(0.71-1.88)	1.10 (1.02-1.18)	1.19 (1.08-1.30)	1.52 (0.92-2.51)	1.15 (1.10-1.20)
F90-F98: Behavioural and emotional disorders with onset usually occurring in childhood and adolescence	10.6% (35)	11.2% (37)	12.7% (42)	14.2% (47)	15.4% (51)	1.01 (0.48-2.11)	0.81 (0.70-0.95)	(0.76-1.98)	1.11 (1.00-1.23)	1.23 (1.07-1.41)	1.01 (0.49-2.12)	1.11 (1.05-1.17)

Table 3. Analysis of the access to health / social services in ASD patients and Odds ratio (OR) and corresponding confidence intervals from logistic regression

	Age (years) % (N.)					Female vs Male	Age as categorical OR (95%CI)				Age as continuous OR (95%CI)	
	16	17	18	19	20		16 vs 18	17 vs 18	19 vs 18	20 vs 18	Female vs Male	Age effect
Global access	46.5% (154)	58.6% (194)	68.0% (225)	57.4% (190)	54.1% (179)	1.40 (0.95-2.07)	0.47 (0.35-0.64)	0.73 (0.56-0.96)	0.55 (0.42-0.72)	0.44 (0.33-0.59)	1.36 (0.92-2)	0.97 (0.9-1.06)
Visit neuropsychiatry as outpatient	15.4% (51)	25.1% (83)	30.8% (102)	10.0% (33)	5.4% (18)	1.19 (0.77-1.85)	0.47 0.34-0.67)	0.79 (0.59-1.07)	0.25 (0.17-0.36)	0.12 (0.07-0.20)	1.15 (0.76-1.74)	0.76 (0.69-0.84)
Visit Neurology as outpatient	4.5% (15)	3.3% (11)	4.8% (16)	6.6% (22)	10.6% (35)	1.66 (0.87-3.19)	1.11 (0.55-2.22)	0.78 (0.38-1.60)	1.47 (0.83-2.61)	2.52 (1.45-4.38)	1.68 (0.87-3.22)	1.29 (1.10-1.53)
Visit Psychiatry as outpatient	12.7% (42)	10% (33)	13.6% (45)	13.6% (45)	14.8% (49)	0.95 (0.64-1.41)	0.97 (0.62-1.50)	0.75 (0.48-1.19)	1.01 (0.65-1.57)	1.07 (0.70-1.64)	0.94 (0.64-1.40)	1.05 (0.94-1.17)
Test as outpatient	6.6% (22)	6.6% (22)	8.5% (28)	3.0% (10)	1.8% (6)	1.05 (0.59-1.87)	0.78 (0.42-1.46)	0.78 (0.45-1.33)	0.33 (0.16-0.71)	0.20 (0.08-0.46)	1.06 (0.60-1.87)	0.76 (0.65-0.87)
Rehabilitation as outpatient	19.9% (66)	20.2% (67)	16.9% (56)	3.9% (13)	3.9% (13)	1.09 (0.65-1.83)	1.38 (0.97-1.96)	1.33 (0.99-1.79)	0.20 (0.11-0.35)	0.19 (0.11-0.34)	1.09 (0.65-1.81)	0.62 (0.56-0.69)
Psychological support as outpatient	15.1% (50)	13.3% (44)	12.1% (40)	6.3% (21)	3.3% (11)	1.74 (1.02-2.98)	1.37 (0.95-1.98)	1.18 (0.81-1.73)	0.47 (0.3-0.73)	0.25 (0.13-0.48)	1.74 (1.02-2.98)	1.37 (0.95-1.98)
ED access[a]	19.3% (64)	22.7% (75)	23.3% (77)	21.5% (71)	19.0% (63)	1.22 (0.82-1.81)	0.91 (0.64-1.28)	1.03 (0.73-1.44)	0.86 (0.62-1.20)	0.72 (0.51-1.01)	1.22 (0.82-1.81)	0.94 (0.86-1.02)
CMHS	0% (0)	0.9% (3)	15.1% (50)	19.3% (64)	20.8% (69)	0.90 (0.5-1.63)	-	-	1.27 (0.97-1.66)	1.33 (0.99-1.78)	0.88 (0.49-1.6)	1.15 (0.99-1.32)
Rehabilitation	17.8% (59)	13.3% (44)	11.5% (38)	4.8% (16)	1.8% (6)	1.33 (0.73-2.43)	1.77 (1.35-2.33)	1.22 (1.02-1.45)	0.38 (0.25-0.59)	0.14 (0.06-0.30)	1.43 (0.79-2.59)	0.61 (0.54-0.68)
Psychiatry visits outpatient and CMHS	12.7% (42)	10.3% (34)	17.8% (59)	23.6% (78)	25.4% (84)	1.00 (0.66-1.52)	0.78 (0.52-1.16)	0.57 (0.37-0.86)	1.39 (1.02-1.9)	1.48 (1.08-2.02)	0.99 (0.65-1.5)	1.22 (1.11-1.35)
Hospital admission	16.9% (56)	22.4% (74)	16.9% (56)	19.3% (64)	16.0% (53)	1.12 (0.75-1.66)	1.42 (0.98-2.05)	1.80 (1.25-2.59)	1.11 (0.78-1.59)	0.82 (0.54-1.23)	1.12 (0.75-1.66)	0.86 (0.78-0.94)
Psychiatry ward	1.2% (4)	2.7% (9)	5.7% (19)	8.5% (28)	6.3% (21)	1.24 (0.68-2.28)	0.29 (0.1-0.79)	0.54 (0.26-1.12)	1.44 (0.89-2.33)	0.97 (0.54-1.74)	1.26 (0.69-2.29)	1.28 (1.1-1.49)
Neuropsychiatry ward	8.8% (29)	10.3% (34)	4.5% (15)	0.9% (3)	0.3% (1)	1.89 (0.97-3.7)	3.18 (1.77-5.72)	3.19 (1.84-5.52)	0.18 (0.05-0.59)	0.06 (0.01-0.38)	1.96 (1-3.84)	0.44 (0.38-0.51)
Psychiatry and neuropsychiatry ward	9.4% (31)	10.6% (35)	9.4% (31)	9.4% (31)	6.6% (22)	1.40 (0.85-2.31)	1.48 (0.92-2.40)	1.43 (0.92-2.22)	0.93 (0.59-1.47)	0.59 (0.35-1.01)	1.41 (0.86-2.32)	0.80 (0.7-0.91)
Residential facility	6.6% (22)	6.3% (21)	8.8% (29)	7.3% (24)	6.0% (20)	0.97 (0.45-2.05)	0.82 (0.52-1.30)	0.76 (0.53-1.10)	0.77 (0.54-1.09)	0.66 (0.43-1.01)	1.00 (0.47-2.13)	0.95 (0.81-1.10)
CSS	4.8% (9)[a]	11.1% (29)[a]	18.4% (61)	20.5% (68)	21.8% (72)	1.46 (0.78-2.74)	0.20 (0.1-0.41)	0.51 (0.37-0.7)	1.15 (1-1.32)	1.21 (1.02-1.45)	1.49 (0.81-2.73)	1.33 (1.22-1.45)

[a] Since databases started from 2012 as denominator we included only contributing age after 2012

(Cont'd)

Table 3. (Continue) Analysis of the access to health / social services in ASD patients and Odds ratio (OR) and corresponding confidence intervals from logistic regression

	Age (years) % (N.)						Age as categorical OR (95%CI)				Age as continuous OR (95%CI)	
	16	17	18	19	20	Female vs Male	16 vs 18	17 vs 18	19 vs 18	20 vs 18	Female vs Male	Age effect
All neuroleptic prescriptions [b]	35.6% (118)	39.3% (130)	44.7% (148)	45% (149)	44.1% (146)	1.18 (0.74-1.88)	0.91 (0.74-1.14)	0.93 (0.78-1.10)	0.94 (0.78-1.13)	0.85 (0.68-1.07)	1.18 (0.74-1.89)	0.98 (0.92-1.05)
Antidepressant (N06A)	5.7% (19)	7.9% (26)	10.6% (35)	9.4% (31)	11.2% (37)	2.54 (1.40-4.64)	0.63 (0.40-0.98)	0.78 (0.54-1.15)	0.81 (0.58-1.15)	0.99 (0.66-1.50)	2.50 (1.37-4.55)	1.10 (0.98-1.24)
Antipsychotic (N05)	27.8% (92)	30.8% (102)	33.8% (112)	34.1% (113)	34.7% (115)	0.57 (0.34-0.96)	1.04 (0.72-1.49)	1.01 (0.75-1.36)	0.92 (0.69-1.22)	0.91 (0.65-1.27)	0.57 (0.34-0.96)	0.97 (0.87-1.07)
Anxiolytic (N05B, N05CD, N05CF)	0.9% (3)	1.8% (6)	1.5% (5)	1.5% (5)	1.5% (5)	3.63 (0.84-15.61)	0.70 (0.24-2.04)	1.48 (0.76-2.85)	0.91 (0.34-2.42)	1.06 (0.43-2.66)	6.00 (1.37-26.24)	1.06 (0.80-1.41)
Antiepileptic (NO3A)	16.3% (54)	16.3% (54)	20.8% (69)	23.0% (76)	23.9% (79)	1.22 (0.71-2.08)	0.91 (0.72-1.16)	0.84 (0.68-1.03)	1.11 (0.92-1.34)	1.13 (0.90-1.41)	1.22 (0.72-2.08)	1.06 (0.99-1.13)
AHDH prescriptions (NO6BA)	0.6% (2)	0.6% (2)	0.6% (2)	0% (0)	0.3% (1)							
Risperidone and/or Aripiprazole (N05AX08, N05AX12)	20.2% (67)	21.8% (72)	23.6% (78)	25.4% (84)	24.2% (80)	0.82 (0.49-1.36)	1.14 (0.86-1.52)	1.09 (0.87-1.36)	1.08 (0.89-1.31)	0.97 (0.76-1.23)	0.81 (0.48-1.34)	0.96 (0.89-1.04)
Risperidone (N05AX08)	15.7% (52)	15.4% (51)	15.7% (52)	15.4% (51)	15.4% (51)	0.54 (0.31-0.94)	1.32 (0.97-1.80)	1.15 (0.89-1.48)	0.93 (0.72-1.20)	0.90 (0.67-1.20)	0.54 (0.31-0.94)	0.91 (0.83-0.99)
Aripiprazole (N05AX12)	5.1% (17)	8.5% (28)	10.3% (34)	11.5% (38)	10.9% (36)	1.47 (0.74-2.92)	0.66 (0.40-1.08)	0.99 (0.70-1.40)	1.14 (0.86-1.50)	1.04 (0.73-1.50)	1.47 (0.73-2.94)	1.09 (0.97-1.24)
Valproic acid (N03AG01)	12.7% (42)	10.9% (36)	15.4% (51)	16.3% (54)	18.1% (60)	1.02 (0.54-1.92)	1.01 (0.77-1.33)	0.77 (0.58-1.02)	1.04 (0.84-1.30)	1.15 (0.88-1.49)	1.02 (0.55-1.88)	1.04 (0.96-1.13)

[b] ATC code "N" (nervous system) excluding anaesthetics (N01) and analgesics (N02)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3/4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	-
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*6-8*
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	-
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7-8
		(*b*) Describe any methods used to examine subgroups and interactions	7-8
		(*c*) Explain how missing data were addressed	-
		(*d*) If applicable, explain how loss to follow-up was addressed	-
		(*e*) Describe any sensitivity analyses	-
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	-
		(c) Consider use of a flow diagram	-
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8;22
		(b) Indicate number of participants with missing data for each variable of interest	22
		(c) Summarise follow-up time (eg, average and total amount)	-
Outcome data	15*	Report numbers of outcome events or summary measures over time	8-10; 23-25
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	-
		(*b*) Report category boundaries when continuous variables were categorized	-
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	-
Discussion			
Key results	18	Summarise key results with reference to study objectives	15
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14-15
Generalisability	21	Discuss the generalisability (external validity) of the study results	14-15
Other information			12
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.